Hypertension is twice as common in diabetics versus the general population. While the prevalence varies between 10-30% in type 1 diabetic patients, this rate is 40-50% at the time of diagnosis in type 2 diabetics.

- HT is associated with the other components of metabolic syndrome in type 2 diabetes.
- HT is usually an indicator of nephropathy in type 1 diabetes and may lead to the progression of renal pathology.

Other reasons of HT in patients with diabetes:

- Coincidental HT which occurs at the same time with diabetes and usually due to other reasons (such as essential HT, isolated systolic HT, HT due to renal scar formation in patients with recurrent pyelonephritis)
- HT due to diabetogenic and anti-hypertensive drugs (K⁺-depleting chlortalidone, high-dose thiazide diuretics, high dose β-blockers, α-blocker/diuretic combinations, glucocorticoids that cause both HT and diabetes, and combined oral contraceptives)
- Endocrine diseases (acromegaly, Cushing syndrome, pheochromocytoma)

Association of diabetes and HT:

- Central obesity
- Atherogenic lipid profile (low HDL cholesterol, high triglyceride levels, increased small-dense LDL-cholesterol levels)
- Hyperinsulinemia and insulin resistance
- Endothelial dysfunction
- Hyperuricemia
- Increased markers of inflammation (e.g. CRP)
- Loss of nocturnal BP reduction (non-dipping HT)
- Left ventricular hypertrophy
- Metabolic factors, such as CAD at an early age play a determining role.

Many guidelines about assessment of HT have been published over the past few years. HT guidelines have been revised based on ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) results, described recently, and JNC-7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure) guidelines, including the rules of approach to and prevention of HT in general population in accordance with the principles of evidence-based medicine, have been published. BP classification has been determined by considering the age and CAD risk in this guideline, and each 10-20 mmHg increase has been reported to be associated with a doubling of CV risk. BP classification according to JNC-7 is given in Table 16.1.
After JNC, American Society of Hypertension (ASH), in its meeting in 2005, has proposed to take into account BP values with CV risk factors and target organ damage in the new classification of HT (Table 16.2).

### Table 16.1 JNC-7 Classification of hypertension

<table>
<thead>
<tr>
<th>Category</th>
<th>Normal BP (sBP≤120, dBP≤80 mmHg)</th>
<th>Occasionally rising BP (sBP 140-160, dBP 80-100 mmHg)</th>
<th>Consistently high BP (sBP 140-160, dBP 80-100 mmHg) or progressive CVD</th>
<th>Continuous and obvious high BP (sBP≥160, dBP≥100 mmHg) or advanced CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Descriptive category</strong></td>
<td>Normal BP (sBP≤120, dBP≤80 mmHg) or rarely higher, but no finding of CVD.</td>
<td>Occasionally rising BP (sBP 140-160, dBP 80-100 mmHg) for early signs of CVD</td>
<td>Consistently high BP (sBP 140-160, dBP 80-100 mmHg) or progressive CVD</td>
<td>Continuous and obvious high BP (sBP≥160, dBP≥100 mmHg) or advanced CVD</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong> (age, gender, lipids, BMI, smoking, diabetes, family history)</td>
<td>No or few</td>
<td>Various</td>
<td>Many</td>
<td></td>
</tr>
<tr>
<td><strong>Markers of early disease</strong> (Microalbuminuria or BP response to exercise/stress)</td>
<td>No</td>
<td>Usually present</td>
<td>Always present</td>
<td>Always present and in progressive character</td>
</tr>
<tr>
<td><strong>Target organ diseases</strong> (Heart, arteries, kidney, eye)</td>
<td>No</td>
<td>No</td>
<td>Early signs present</td>
<td>Obvious, CVD present or not present</td>
</tr>
</tbody>
</table>

16.1 CLINICAL ASSESSMENT OF HYPERTENSIVE PATIENTS WITH DIABETES

Effective treatment of HT can prevent diabetes and complications.

- According to evidence-based medicine recommendations for HT treatment in diabetes, goals have been transformed and 140/90 mmHg value in the 1990s declined to 130/80 mmHg.

- United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that a 10 mmHg reduction in sBP was associated with a 24% lower rate of complications related to diabetes, a 37% decline in the risk of microvascular complications, and a 14% lower risk of stroke.

- However, in the same trial a 1% reduction in A1C was associated with a 24% lower rate of complications related to diabetes, a 37% decline in the risk of microvascular complications, and a 16% lower risk of stroke.

#### Table 16.2 New hypertension classification according to ASH 2005 recommendations

<table>
<thead>
<tr>
<th>Classification</th>
<th>Normal BP (sBP≤120, dBP≤80 mmHg)</th>
<th>Occasionally rising BP (sBP 140-160, dBP 80-100 mmHg)</th>
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<tr>
<td><strong>Cardiovascular risk factors</strong> (age, gender, lipids, BMI, smoking, diabetes, family history)</td>
<td>No or few</td>
<td>Various</td>
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<td>Always present and in progressive character</td>
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<td><strong>Target organ diseases</strong> (Heart, arteries, kidney, eye)</td>
<td>No</td>
<td>No</td>
<td>Early signs present</td>
<td>Obvious, CVD present or not present</td>
</tr>
</tbody>
</table>

16.1 CLINICAL ASSESSMENT OF HYPERTENSIVE PATIENTS WITH DIABETES

When a patient with diabetes is diagnosed with HT:

- The degree of HT
- Secondary causes of HT (renal, endocrine and drug-induced)
- Tissue damage related to HT (left ventricular hypertrophy, CVD, heart failure, peripheral vascular disease, renal failure, and fundus changes) should be investigated.
- Also other risk factors associated with CVD such as smoking, hyperlipidemia, poor glycemic control, family history of CAD should be asked.
- Standing or supine BP measurement, signs of left ventricular hypertrophy, heart failure, peripheral pulses (renal murmur and radio-femoral delay) and signs of an underlying endocrine or renal disease should be sought in physical examination.

Laboratory investigations:

- ECG (left ventricular hypertrophy, ischemic changes, arrhythmias)
- Teleradiography (heart shadow size, left ventricular dilation)
- Fundus examination
- Urine analysis
16.2 TREATMENT OF HYPERTENSION IN DIABETES

Hypertensive patients with diabetes should be encouraged to reach target BP values ≤130/80 mmHg. The lowest BP (≤120/70 mmHg) as tolerated should be reached in appropriate cases if they are not at risk of severe hypotension. Lifestyle interventions to reduce BP should be considered, including achieving and maintaining a healthy weight, doing exercise and

16.2.1 Non-pharmacological treatment

- Patients with a sBP of 130-139 mmHg or dBP of 80-89 mmHg should be followed for maximum period of three months with lifestyle and behavioral education.
- Lifestyle changes must be planned and implemented primarily in the treatment process.
- The relationship between HT, obesity and salt intake is well-known.
- Weight loss and salt restriction can decrease BP. But there are no controlled trials documenting the roles of diet and exercise in the treatment of HT.
- However, it is recommended to increase the consumption of fresh vegetables, fruit and low fat products.
- In the diet of hypertensive patient with diabetes, the recommended adequate intake for Na+ is 3.80-5.85 g/day and for K+ is >5.9 g/day.
- There is not a clear-cut clinical trial documenting the support of Ca²⁺ and Mg²⁺ in hypertensive persons.
- Dynamic activities at moderate intensity (walking, jogging, bicycling, swimming) are recommended ≥4 days a week for 30-60 minutes.
- Weight loss is a crucial factor in lifestyle changes. Patients with HT, with BMI >25 kg/m², should lose weight.
- Waist circumference should be <102 cm in men and <88 cm in women (IDF definitions of waist circumference for European men <94 cm and women <80 cm).
- Weight loss increases the effectiveness of pharmacological treatment.
- Also in terms of stress factors, the use of relaxation techniques and reduced alcohol consumption (maximum 4 drinks/week for men and 2 drinks/week for women) are recommended.
- If target HT values cannot be reached despite lifestyle modifications and behavioral training, drug therapy should be initiated.

16.2.1 Non-pharmacological Treatment

- If sBP ≥140 mmHg and dBP ≥90 mmHg, pharmacological treatment should be initiated concurrently with lifestyle recommendations.
- The agents shown to be beneficial in pharmacological treatment of patients with diabetes and HT in controlled trials are ACE-I, ARB, low dose thiazide diuretics, and β-blockers and calcium channel blockers in CAD patients.
- All guidelines recommend life-style changes as initial treatment, then a renin angiotensin system (RAS) antagonist, ACE-I or ARB, in patients with albuminuria.
- In patients without albuminuria any of the options is reported to be useful.
- Progression of clinical nephropathy can be slowed through the use of ACE-I, regardless of HT, in patients with type 1 diabetes.
- In the presence of HT the progression of microalbuminuria can be delayed with ACE-I or ARB in type 2 diabetics.
- In people with type 2 diabetes and HT, microalbuminuria or clinical renal failure (serum creatinine >1.5 mg/dL), ARBs may delay progression to end-stage renal disease.
- If a RAS system blocking agent cannot be tolerated, it can be substituted with another one.
- A 24-h ambulatory BP monitoring is recommended in patients with suspicious white-coat HT.
- In addition, β-blockers are recommended for patients with previous myocardial infarction or angina, and ACE-I or diuretics for those with heart failure, and β-blocker + thiazide combinations should be monitored carefully because of the negative effects on metabolic control.
- As the duration of HT gets longer, it becomes difficult to control BP. Patients with diabetes use a mean of 3.2 different types of drugs to reach the target BP values in the treatment of HT. This has been shown in several studies.
16.2.2 Pharmacological Treatment

- Target BP should be 110-129/65-79 mmHg in pregnant women with chronic HT and diabetes.
- While these values have long-term benefits to mother, lower values may have negative effect on fetal growth.
- ACE-Is and ARBs are contraindicated in pregnancy as they can cause fetal injury.
- Chronic use of diuretics may impair utero-placental perfusion by reducing maternal plasma volume.
- Methyldopa, labetolol, diltiazem, clonidine and prazosin are safe and effective agents in pregnancy.

The advantages and disadvantages of drugs used to treat HT in diabetic patients are summarized in Table 16.3. The algorithm of HT treatment in patients with diabetes based on JNC-7 guideline and ALLHAT study is outlined in Figure 16.1.

Table 16.3 Drug classes in treatment of hypertension in diabetes

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Cheap</td>
<td>Hyperglycemia, dyslipidemia, sexual dysfunction</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Cheap, post-MI benefits have been shown.</td>
<td>May suppresses the symptoms of hypoglycemia, sexual dysfunction</td>
</tr>
<tr>
<td>ACE-Is</td>
<td>Specific effects on nephropathy</td>
<td>Cough, hyperkalemia</td>
</tr>
<tr>
<td>ARBs</td>
<td>Specific effects on nephropathy</td>
<td>Expensive</td>
</tr>
<tr>
<td>CCBs</td>
<td>Effective</td>
<td>Edema</td>
</tr>
</tbody>
</table>

Accordingly:
- Concurrent with lifestyle modification dietary regulation is recommended as initial therapy in order to reach target BP values (<130/80 mmHg).
- For persons with BP ≥130/80 mm Hg despite lifestyle interventions an ACE-I (or an ARB) is recommended.
- Thiazide diuretics should be added if necessary.
- The doses should be increased and additional antihypertensive drugs should be used and if target BP levels are not achieved with standard-dose monotherapy.

Figure 16.1 Antihypertensive treatment algorithm in patients with diabetes

BP: Blood pressure, UAE: Urinary albumin excretion

*The anti-hypertensive treatment algorithm based on JNC-7 and ALLHAT trial is modified from “Joslin’s Diabetes Mellitus 2005.”*
**SEMT RECOMMENDATIONS THE TREATMENT OF HYPERTENSION IN DIABETES**

1. BP should be measured at every diabetes outpatient visit for the assessment of HT (Class D, evidence-based consensus).
2. HT should be diagnosed in people with diabetes according to the current HT guidelines (Class D, evidence-based consensus).
3. Persons with diabetes and HT should be treated to attain sBP <130 mm Hg [Class C, Level 3 evidence (1-3)] and dBP <80 mm Hg [Class B, Level 2 evidence (4,5)].
4. Lifestyle interventions to reduce BP (achieving and maintaining a healthy weight and limiting sodium and alcohol intake) should be initiated concurrently with pharmacological interventions (Class D, evidence-based consensus).
5. For persons with diabetes and normal UAE and without chronic kidney disease, with BP ≥130/80 mm Hg:
   - Any of the following medications is recommended, with special consideration to ACE-Is and ARBs given their additional renal benefits (Class D, evidence-based consensus):
     - ACE-I [Class A, Level 1A evidence (6)]
     - ARB [Class A, Level 1A evidence (7); for non-left ventricular hypertrophy Class B, Level 2 evidence (7)]
     - Dihydropyridine calcium channel blocker (DHP-CCB) [Class B, Level 2 evidence (8)]
     - Thiazide-group diuretics [Class A, Level 1A evidence (8)]
     - If the above drugs are contraindicated or cannot be tolerated, a cardioselective -blocker [Class B, Level 2 evidence (5)] or a non-DHP-CCB [Class B, Level 2 evidence (9)] can be substituted.
   - Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy [Class C, Level 3 evidence (5,8)].
   - Add-on drugs should be chosen from the first-line choices listed above (Class D, evidence-based consensus).
   - For people with diabetes and persistent albuminuria an ACE-I or an ARB is recommended as initial therapy (Class A, Level 1A evidence (10-13)).
   - If BP remains ≥130/80 mm Hg despite lifestyle interventions and the use of an ACE-I or an ARB, additional antihypertensive drugs should be used to obtain target BP (Class D, evidence-based consensus).
6. For persons with diabetes and a normal UAE rate, without chronic kidney disease but with isolated systolic HT:
   - An ACE-I [Class B, Level 2 evidence (6)]
   - An ARB [Class B, Level 2 evidence (7)]
   - A thiazide-group diuretic [Class B, Level 2 evidence (8,14)] or
   - Alternatively a long-acting DHP-CCB [Class C, Level 3 evidence (15)] can be used.
7. Alpha-blockers are not recommended as first-line agents for the treatment of HT in persons with diabetes [Class A, Level 1A evidence (16)].

REFERENCES


