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Treatments for Hypertension in Type 2 Diabetes-Non-Pharmacological and Pharmacological Measurements

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1. Introduction

Type 2 diabetes and hypertension are becoming a major worldwide health problem, being associated with increasing prevalence of obesity and excess morbidity and mortality. Furthermore, hypertensive patients with diabetes or obesity are more predisposed to target organ damage, resulting stringent targets for blood pressure control [1-4]. Focusing on the close associations between obesity, hypertension and diabetes, the NHANES [5, 6] and the Behavioral Risk Factor Surveillance System (BRFSS) [7] studies showed very close relationships between the prevalence of obesity, hypertension, and diabetes (**Figure 1**). The Framingham Heart Study [8] demonstrated that diabetic subjects were at 2-fold higher risk mortality, comprising both cardiovascular and non-cardiovascular mortality. Evidence from these epidemiological studies indicates that obesity and weight gain are associated with an increased risk of hypertension [5-7, 9] and type 2 diabetes [7, 9, 10], and that intentional weight loss reduces the risk that currently overweight individuals will develop hypertension [11, 12] or type 2 diabetes [13].

The clustering of cardiovascular risk factors associated with (abdominal) obesity is well established. Type 2 diabetes, itself, contributes strongly to mortality, morbidity, and cardiovascular risk, including myocardial infarction [14], cardiac events [15-18], stroke, atherosclerosis [19-21] and cardiovascular and renal complication [22, 23]. Hypertension is observed twice as frequently in diabetic patients than in the general population, and its prevalence is higher in type 2 diabetes than in type 1 diabetes. Diabetes accompanying cardiovascular diseases such as hypertension is associated with higher mortality and morbidity [24]. The World Health Organization Multinational Study of Vascular Disease in diabetes [17, 18] showed that even in the absence of proteinuria and hypertension, standardized mortality rates were significantly higher in patients with both type 1 and type 2 diabetes compared to those in the general population. Standardized mortality was higher in those with type 1 diabetes compared with type 2 diabetes. Both hypertension and proteinuria in diabetes were associated with a markedly high mortality risk by 11-fold for men with type 1 diabetes, and 5 fold for men with type 2 diabetes. A longer duration of diabetes and hypertension was a stronger predictor of mortality among diabetic and hypertensive patients. Therefore, those hypertensive patients with concomitant diabetes

mellitus, or strong lifestyle or dietary factors to predict the development of type 2 diabetes such as obesity, should be treated as a matter of priority in order to prevent subsequent cardiovascular complications [25]. Importantly, the blood pressure goals of antihypertensive treatments is much lower in hypertensive patients with diabetes (<130/80 mmHg) compared to hypertensive patients without complications [1, 4] (Table 1).

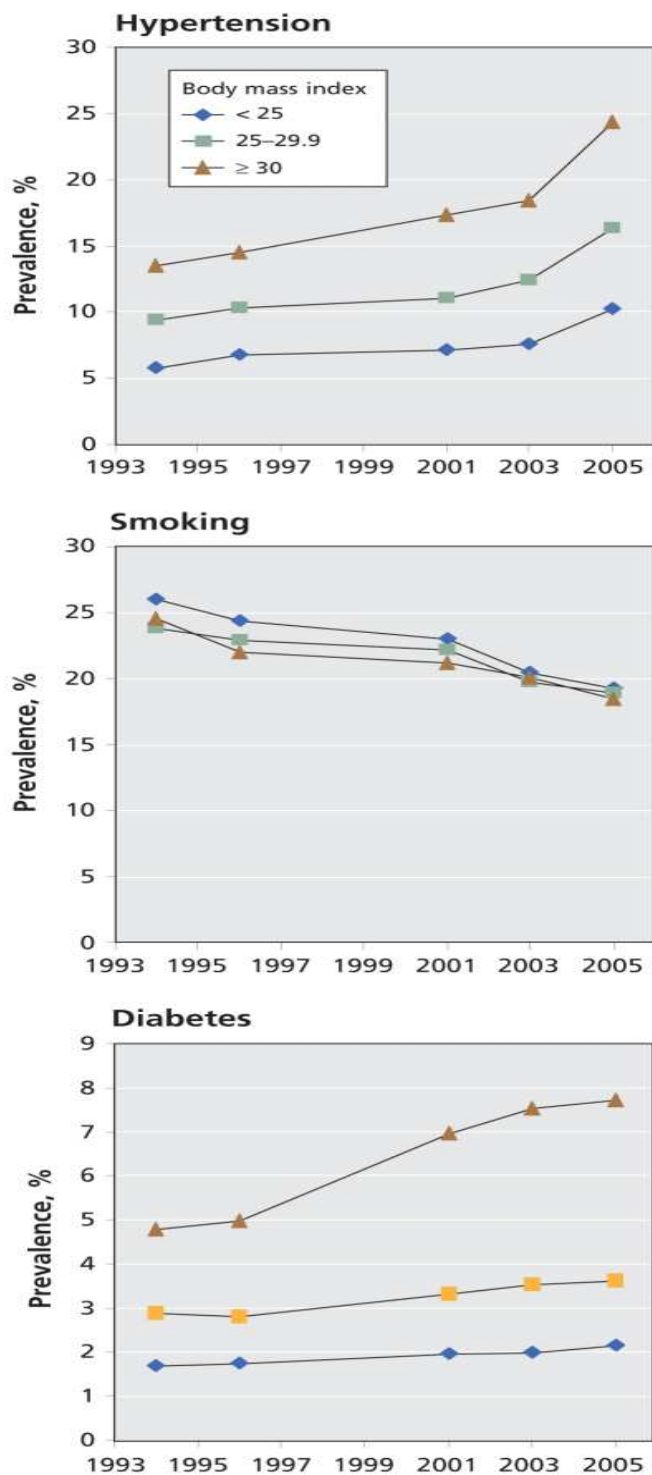


Fig. 1. Increased prevalence of diabetes and hypertension. [Reference 7]

	Clinic blood pressure	Home blood pressure
Young/middle-aged persons	<130/85 mmHg	<125/80 mmHg
Elderly persons	<140/90 mmHg	<135/85 mmHg
Diabetic patients with kidney disease	<130/80 mmHg	<125/75 mmHg
Diabetic Patients after myocardial infarction	<130/80 mmHg	<125/75 mmHg
Diabetic patients with cerebrovascular disorders	<140/90 mmHg	<136/85 mmHg

Note: As the criteria for hypertension include a clinic blood pressure (BP) of 140/90 mm Hg and a home BP of 135/85 mm Hg, the differences between clinic and home BP (5 mm Hg) were simply applied to the clinic BP in each condition and derived provisional target home BP levels. BP, blood pressure. [Reference 2]

Table 1. Expected target blood pressure levels of antihypertensive treatment

The selection of the most suitable pharmacological treatments for those hypertensive patients with type 2 diabetes is governed to a degree by the knowledge of the physiological mechanisms underpinning the specifics of the conditions. Insulin resistance, stimulated renin-angiotensin-aldosterone system (RAAS), sympathetic nervous activation, and leptin resistance (hyperleptinemia) [26-29] are observed very frequently in type 2 diabetes, hypertension and obesity, and these factors appears to play an important role on the onset and developments of these conditions [23, 30, 31].

The first line of treatments for obesity, type 2 diabetes, and hypertension are weight loss with a lifestyle modification such as low caloric diet and exercise [32-34], or, in those with more severe obesity or inability to undertake an exercise program, or bariatric surgery. Perhaps the most important and difficult aspect in controlling obesity is avoiding weight regain [35, 36]. Anti-obesity drugs such as orlistat, sibtramine, rimonabant, and contrave [37-40] have been developed, however these drugs were recently withdrawn from the markets in Europe, the United States and Australia due to serious side effects. Additionally, leptin administration (pegylated recombinant leptin, PEG-OB; recombinant methionyl human leptin, r-metHu Leptin) has been investigated for effects of weight loss and their mechanisms, however, it has not yet been used clinically.

Despite the benefits of lifestyle modifications, additional pharmacological treatment for the management of hypertension is frequently needed. However, the choice of an antihypertensive drug is controversial for patients with associated with diabetes. Lind *et al.* [41] have previously summarized these metabolic effects with long-term antihypertensive treatments. Studies suggest that treatment with different antihypertensive drug classes may have varied effects on glucose and lipid metabolism [42]. In this context, it would be important to choose more beneficial antihypertensive drugs that have less adverse metabolic effects and to achieve stricter blood pressure goals for hypertension associated with type 2 diabetes and obesity.

An integrated cardiovascular risk management approach should be adopted. Aggressive blood pressure control is important, particularly in patients at high cardiovascular disease risk such as those with diabetes. Moreover, well-tolerated antihypertensive agents with protective benefits beyond blood pressure lowering, if this can be achieved, should be

adopted [43]. Recently, many large scale clinical studies have shown that angiotensin II receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACE inhibitors) are highly efficacious, well-tolerated antihypertensive agents [44, 45]. More disputed is whether there are additional benefits, beyond blood pressure lowering, leading to greater cardiovascular protection in obesity-related hypertension, metabolic syndrome, and diabetes. Recently, renin-inhibition with Aliskiren has been reported to impart an ameliorative effect on insulin resistance in type 2 diabetic mice [46]. Calcium channel blockers (CCBs), especially newer longer-acting dihydropyridines, may also provide favourable metabolic effects by improving insulin sensitivity and stimulated RAAS and sympathetic nervous activation in diabetes patients [47-49].

In this review, we discuss i) mechanisms of hypertension in type 2 diabetes; ii) the importance of weight loss as a non-pharmacological treatments for type 2 diabetes and hypertension; iii) achieving blood pressure reduction goals for hypertension with diabetes (JNC-7 and JSH 2009), and iv) pharmacological treatments for hypertension in type 2 diabetes.

2. Characteristics of hypertension in obesity and type 2 diabetes: insulin resistance, elevated sympathetic nervous activity, and stimulated the renin-angiotensin-aldosterone system (RAAS) (Figure 2)

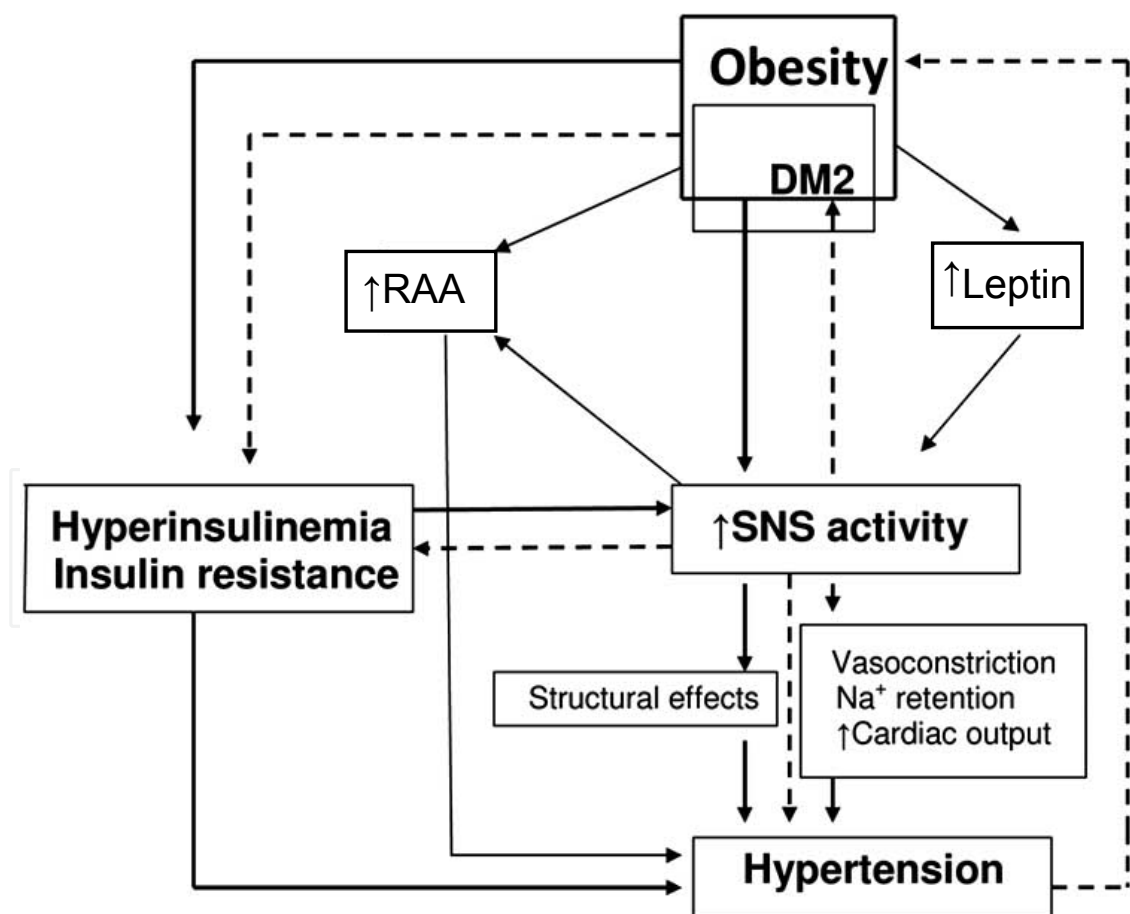


Fig. 2. Relationships between insulin resistance, sympathetic activation and stimulated renin-angiotensin-aldosterone system (RAA) in type 2 diabetes and hypertension. [Reference 22]

Data from many epidemiological and clinical studies has identified a close relationship between elevated sympathetic nervous system activity and insulin resistance / hyperinsulinemia in obesity (**Figure 2**) [22, 30, 50]. Several studies of longitudinal design have examined the effect of body weight changes (weight loss or weight gain) on sympathetic nervous system activity and insulin sensitivity (fasting plasma insulin levels and homeostatic model assessments of insulin resistance (HOMA-IR)). Elevations in sympathetic nervous activity and insulin levels during weight gain [51, 52] and reductions of sympathetic nerve activity and insulin levels during weight loss [11, 33, 53] have been observed. These longitudinal studies have clearly shown that elevated sympathetic activity and insulin resistance are closely linked to obesity (weight gain), the onset of obesity and the maintenance of obesity. Similarly, sympathetic activation and insulin resistance are strongly linked to the onset and development of hypertension [51, 52] and diabetes [54]. Furthermore, stimulation of the renin-angiotensin-aldosterone system (RAAS) is frequently demonstrated in obesity and hypertension [55, 56], and may be related to insulin resistance either via direct or indirect mechanisms [57, 58].

2.1 Insulin resistance

Ferrannini *et al.* was the first investigator who reported insulin resistance or hyperinsulinemia in obese hypertensive patients [59, 60] as well as lean hypertensive subjects [61] over 20 years ago. They observed in obese subjects that the insulin response to oral glucose was twice as high in the hypertensive patients as in the normotensive subjects, yet the glucose incremental area was 3-fold higher in the former than in the latter, thus indicating more severe insulin resistance in obese hypertensive patients. In the hypertensive group, 2-hrs plasma insulin was strongly correlated with systolic BP levels [61]. In obese hypertensive patients, the occurrence of hypertension marks the presence of additional hyperinsulinemia and insulin resistance, independent of any impairment of glucose tolerance [60].

The EGIR-RISC study (The European group for the study of insulin resistance: relationship between insulin sensitivity and cardiovascular disease risk) studied insulin resistance and cardiovascular disease risk in 1500 healthy, middle-aged individuals over a 3-10 year period. Glucose tolerance and insulin sensitivity were measured with using an oral glucose tolerance test and the euglycemic insulin clamp. The EGIR-RISC Study demonstrated the importance of insulin resistance in the development of cardiovascular disease and diabetes, and has implications for the development of prevention and treatment strategies [62]. The EGIR-RISC study's documentation of strong relationships of blood pressure to both insulin action and circulating insulin levels is compatible with the distinct influences on BP by insulin resistance and compensatory hyperinsulinemia [63].

2.2 Stimulated renin-angiotensin-aldosterone system

Angiotensin II (Ang II) produced in vessel walls disrupts the regulation of physiologically active substances by impairment of endothelium cell function [56]. Ang II mediated production of reactive oxygen species (ROS) promotes growth factors, cytokines and chemotactic factors relating to atherosclerosis [65]. A high level of insulin, as occurs in insulin resistance states, induces the activation of the tissue RAAS in blood vessels and the heart, and leads to an overproduction of Ang II in these tissues [33, 58]. High levels of insulin directly activate the expression and production of angiotensin, cell growth through

the angiotensin I receptor and the conversion of Ang I to Ang II in vascular smooth muscle cells. Although the mechanisms leading to the initial activation of tissue Ang II in high-risk conditions such as type 2 diabetes and hypertension, RAAS blocking agents such as angiotensin converting enzyme inhibitors (ACE inhibitors) and Ang II receptor blockers (ARBs), inhibits the multi-factorial effects of Ang II and reduce the frequency of cardiovascular events as observed in the HOPE and LIFE studies [58, 66, 67]. The HOPE Study (the Heart Outcomes Prevention Evaluation study) showed that high plasma rennin activity is an independent predictor of major vascular events and mortality in a stable population of high-risk patients with atherosclerosis and/or diabetes [58]. The RAAS associated with insulin resistance and sympathetic nerve activation plays an important role of hypertension in type 2 diabetes.

2.3 Sympathetic nervous activation

Energy intake stimulates hyperinsulinemia and sympathetic nerve activity resulting in blood pressure elevation.. Insulin-mediated sympathetic nerve stimulation in obese subjects is a compensatory mechanism aimed at restoring the energy balance by increasing the metabolic rate [22, 30]. Masuo *et al.* [51, 52] have shown in a longitudinal study that heightened sympathetic nervous activity (as indicated by plasma norepinephrine levels) may be a prime mover for future weight gain and blood pressure elevations in originally nonobese, normotensive subjects, and that insulin resistance may be an ancillary factor. During weight loss studies, reductions in plasma norepinephrine followed by reductions in HOMA-IR were observed [33, 34, 53]. These observations show, at least, that the sympathetic nervous system activity associated with insulin resistances play a major role in the onset and development of hypertension with type 2 diabetes associated with obesity.

3. Treatments for obesity

3.1 Lifestyle modification for weight loss

Weight loss is recommended as the first-line treatment for obesity-induced hypertension and type 2 diabetes. The objective of treatment for obesity is both to reduce the high risk of cardiovascular events and to prevent the developments of hypertension and type 2 diabetes [68]. A limited number of epidemiological studies have shown that intentional weight loss and fat loss may reduce the all-cause mortality rate [69]. The US Diabetes Prevention Program [70] and the Oslo Diet and Exercise Study [71] have shown marked clinical benefits with lifestyle intervention, and modest weight loss, on the resolution of the metabolic syndrome and type 2 diabetes. Cohort studies with lifestyle modifications [72] and case control studies with bariatric surgeries [73, 74] provide some evidence that intentional weight loss has long-term benefits on all cause mortality in overweight adults. In a cohort of patients enrolled in a cardiac rehabilitation program, weight loss was associated with favourable long-term outcomes on the composite end-point of mortality and acute cardiovascular events (fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, emergent revascularization for unstable angina pectoris, and congestive heart failure) [75]. Maintaining weight loss is often the greatest challenge, but, many clinical studies have demonstrated that weight loss associated with life-style modification adds to the efficacy of antihypertensive pharmacological treatment [11].

Ribeiro *et al.* [76], Trombetta *et al.* [77] and Tonacio *et al.* [78] compared the blood pressure lowering effects and forearm blood flow between a low caloric diet and exercise, and they observed that only exercise significantly increased forearm blood flow. Recently, Straznicky *et al.* [79] and Masuo *et al.* [80] have shown that a low caloric diet and exercise exert different effects on insulin resistance, the RAAS, and sympathetic nervous activity in obese hypertensive subjects, even though similar weight loss were observed.

3.2 Bariatric surgery

Gastric bypass and adjustable gastric banding are the two most commonly performed bariatric procedures for the treatment of morbid obesity or obesity which is resistant to lifestyle modification such as a low caloric diet plus exercise. Dixon *et al.* [74] showed that a gastric banding induced significant weight loss and resulted in better glucose control and less need for diabetes medication than conventional approaches to weight loss and diabetes control in a randomized controlled study in obese subjects with recently diagnosed type 2 diabetes. Nguyen *et al.* [81] and other investigators [82, 83] compared the effects on weight loss, mortality, morbidity and changes in quality of life in subjects with either gastric banding or gastric bypass. The percent of excess weight loss at 4 years was higher in the gastric bypass group compared to the gastric banding group. Postoperative HOMA-IR correlated with % weight loss [84]. Concurrent with restoration of insulin sensitivity and decreases in plasma leptin were dramatic decreases in skeletal muscle transcript levels of stearoyl coenzyme-A desaturase and pyruvate dehydrogenase kinase-4 at 3 and 9 months after gastric banding and a significant decrease in peroxisome proliferation activated receptor- α -regulated genes at 9 months. Gumbs *et al.* [84] speculated that decrease in fat mass caused by bariatric surgery significantly affected circulating adipocytokines, which favourably impact on insulin resistance. Improvements in glucose metabolism and insulin resistance following bariatric surgery result in the short-term from decreased stimulation of the entero-insular axis by restricted calorie intake and in the long-term by decreased fat mass resulting changes in release of adipocytokines. Leptin levels drop and adiponectin levels rise following laparoscopic adjustable gastric banding, gastric bypass and biliopancreatic diversion. These changes correlate with weight loss and improvement in insulin sensitivity [84].

All forms of weight loss surgery (bariatric surgery) lead to calorie restriction, weight loss, decrease in fat mass, improvement in insulin resistance and type 2 diabetes mellitus [84]. Left ventricular relaxation impairment, assessed by tissue Doppler imaging, normalized 9 months after surgery [85]. Laparoscopic gastric bypass and gastric banding are both safe and effective approaches for the treatment of morbid obesity, but gastric bypass surgery seems to have better early weight loss and more rapid ameliorative effects on insulin resistance and adipocytokines, muscle metabolism and left ventricular function, however effects the long term effects with similar sustained weight loss are unknown.

3.3 Pharmacological treatments for obesity (Orlistat, Sibtramine, and Rimonabant- Currently withdrawn in Europe, United States and Australia)

Pharmacological treatment for the management of obesity is primarily aimed at weight loss, weight loss maintenance and risk reduction. Anti-obesity agents decrease appetite, reduce absorption of fat or increase energy expenditure. Recently, anti-obesity drugs such as orlistat, sibtramine and rimonabant have been developed placed on markets, however, the

latter two were withdrawn from markets in Europe and in the United States due to serious adverse events including psychiatric and cardiovascular related concerns. Lorcaserin, taranabant, topiramate and bupropion with naltrexone are currently on phase III trials with demonstrated significant weight loss compared to placebo at more than 12 months. Some pharmacotherapies have also demonstrated clinical benefits without any side effects, however, further studies are required for a long-term safety [86]. Recently, contrave, a combination of two approved drugs of bupropion and naltrexone, completed Phase III trials with significant weight loss and was approved by FDA in 2010, but FDA declined to approve contrave due to serious cardiovascular adverse events in 2011 [86]. Importantly, obesity is, at least, in part, determined by genetic backgrounds [87], suggesting that a genetic approach to limiting obesity may find a place in the future.

3.4 Leptin administration (pegylated recombinant leptin; PEG-OB, and recombinant methionyl human leptin; r-methHu Leptin)

Lejeune *et al.* [88], Hukshorn *et al.* [89] and Westerterp-Plantenga, *et al.* [90] investigated the effect of weight loss and dietary restraint during and following weekly subcutaneous pegylated recombinant leptin (PEG-OB protein) administration in overweight men. Although treatment with PEG-OB protein led to a significantly greater body weight loss, energy expenditure, and dietary restraint, weight regain (rebound) was faster and stronger in subjects treated with PEG-OB compared to placebo. Asakawa *et al.* [91] administered leptin intraperitoneally for 5 days in ob/ob mice. Intraperitoneal leptin administration caused significantly body weight loss of 13.2%. Further, an additional ameliorative effect on anxiety was found with leptin administration. This finding, in ob/ob mice, appears not be relevant to the human condition. PEG-OB protein may theoretically work on human for weight loss, however, at this juncture there are few clinical studies available.

4. Pharmacological treatments for the metabolic syndrome as a precursor of type 2 diabetes

The metabolic syndrome, which may be considered to be the precursor of type 2 diabetes, increases the risk of cardiovascular and renal events in hypertension. It has been associated with a wide range of classical and new cardiovascular risk factors as well as with early signs of subclinical cardiovascular and renal damage. The National Cholesterol Education Program's Adult Treatment Panel III definition uses easily measured clinical findings of increased abdominal circumference, elevated triglycerides, low high-density lipoprotein-cholesterol, elevated fasting blood glucose and/or elevated blood pressure. Three of these five are required for diagnosis. It should be noted that other definitions of metabolic syndrome focus more on insulin resistance and its key role in this syndrome [22] (**Table 2**). Metformin has been shown to be helpful in subjects with metabolic syndrome or diabetes [92]. Atabek *et al.* [93] examined whether metformin treatment for 6 months was effective in reducing body weight and hyperinsulinemia, whilst also ameliorating insulin sensitivity indices in 120 obese adolescents with hyperinsulinemia. Before treatment, there were no significant differences between the metformin group and control group in terms of anthropometric data, metabolic parameters, and blood pressure levels. After metformin, there was a significant decline in body mass index, fasting insulin, 120 min insulin levels and HOMA-IR and a significant increase in the fasting glucose/insulin ratio. With regards

to insulin sensitivity indices between the metformin treated and control groups, the metformin group displayed significantly improved metabolic control at the end of the study. These findings show the efficacy of metformin for obesity and insulin resistance (metabolic syndrome) in obese adolescents. While metformin has also been shown to prevent weight gain and improve blood glucose levels in hypertensive patients who received combination therapy of calcium antagonist (nitrendipine) and beta-blocker (atenolol) [94], in combination with drugs blocking the rennin-angiotensin system (ACEI or ARB), metformin may be associated with lactic acidosis and acute renal failure in patients with reduced renal function [95].

Whilst thiazolidinedione drugs (TZDs) may prove useful in the metabolic syndrome, or type 2 diabetes, a large concern has been expressed over the cardiovascular risks associated with rosiglitazone and pioglitazone [96]. Hsiao *et al.* [97] performed retrospective cohort study of 473,483 newly diagnosed patients with type 2 diabetes in order to evaluate the associations between oral antihyperglycemics (TZDs including rosiglitazone and pioglitazone, sulfonylureas, and metformin) with myocardial infarction, congestive heart failure, angina pectoris, stroke and transient ischemic attack. The findings extend the evidence provided further support to data derived from clinical trials that suggested that the disadvantages or harm caused by TZDs, especially rosiglitazone, may outweigh their benefits in patients with type 2 diabetes due to high risk for cardiac events. In addition, although the glycemic efficacy of TZDs are comparable to metformin, adverse effects and higher costs make TZDs less appealing for initial therapy. Among the TZDs, based on cardiovascular safety data, pioglitazone is the preferred choice. In combination with metformin, pioglitazone may be particularly beneficial for patients with metabolic syndrome and diabetes. In those patients who are achieving glycemic goals and tolerating the therapy without apparent complications, rosiglitazone may be continued [97]. Pioglitazone, but not metformin, in patients with type 2 diabetes significantly reduced hepatic lipid and increased adiponectin independent of weight change [98].

5. Pharmacological treatments for hypertension (Figure 3)

Although diabetes mellitus is associated with increased risks of death and cardiovascular events, in the Framingham Heart Study much of this excess risk was attributable to coexistent hypertension [99]. Tight control of blood pressure (BP) significantly reduces cardiovascular morbidity and mortality in hypertensive patients with diabetes. In the United Kingdom Prospective Diabetes Study [100], a 10 mmHg reduction in systolic blood pressure was superior to a 0.7% decrease in glycosylated haemoglobin A1c (HbA1c) with regards to reducing morbidity and mortality [101]. In the Hypertension Optimal Treatment Study [102, 103], the risk of cardiovascular events was decreased by 51% in those patients with type 2 diabetes randomized to the lower BP level. The HOT study demonstrated that monotherapy was successful in only 25-40% of patients, according to the target diastolic blood pressure in diabetic patients, and they were needed at least 2 drugs, average 2.5-3 additional antihypertensive drugs to control blood pressure. [104, 105]. Based on these findings, contemporary treatment guidelines recommend a target blood pressure of <130/80 mmHg for patients with diabetes [106], however, evidence shows that most hypertensive patients with diabetes are very resistant to controlling hypertension and frequently require two or more types of antihypertensive medications in order to achieve blood pressure goals [103, 104, 107, 108].

2. Criteria for Metabolic Syndrome including Insulin Resistance

	WHO	EGIR	NCEP AT III (Expert Panel On Detection Evaluation and Treatment Of High Blood Cholesterol in Adults)	American Heart Association Updated NCEP III
Insulin resistance	Top 25% of population Distribution	Top 25% of population distribution	Not considered	Not considered
Hyperinsulinemia	Not considered	Top 25% of population distribution	Not considered	Not considered
Fasting glucose (mmol/L)	impaired fasting glucose, or impaired glucose tolerance or diabetes	>6.1, but not diabetic	≥6.1	≥5.6 (100 mg/dL) or medications for hyperglycemia
Hypertension (mmHg)	≥160/≥90	≥140/≥90 or on meds. for hypertension	≥130/85 or meds. for hypertension	≥130/85 or medications for hypertension
Central obesity	waist/hip ratio >0.9 (men), >0.85 (women) and/or BMI ≥30kg/m ²	---	---	---
Waist circumference (cm)	Not considered	≥94 (men), ≥80 (women)	>102 (men), >88 (women)	≥102 (men), ≥88 (women)
HDL-cholesterol (mmol/L)	<1.0 or medications for dyslipidemia	<1.0 or medications for dyslipidemia	<1.07 (40 mg/dL, men), <1.25 (50 mg/dL, women)	<1.07 (40 mg/dL, men)
Triglyceride (mmol/L)	<1.0 or medications for Dyslipidemia	>2.0 or medications for dyslipidemia	≥1.695 (150 mg/dL)	≥1.695 (150 mg/dL)
Micro-albuminemia	Present	Not considered	Not considered	Not considered
Criteria	1 of the first two + 2 of other features	1 of the first two + 2 of other features	3 of above	3 of above

BMI, body mass index; EGIR, European Group of the study of Insulin Resistance; NCEP ATPIII, 3rd Recommendations of the Adult Treatment Panel of the National Cholesterol Education Program; HDL-cholesterol, high-density lipoprotein cholesterol. Values in NCEP definition and American Heart Association/Updated NCEP are approximations of values in mg/dL [Reference 31]

Fig. 3. The Guideline for Hypertension Treatments by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) : Algorithm for Treatment of Hypertension [Reference 1]

Class differences in the effects of antihypertensive medications on metabolic indices may therefore be an important consideration when choosing treatment for hypertensive patients with type 2 diabetes. Prospective, randomized studies with antihypertensive drugs have demonstrated differences between classes of drugs regarding effects on insulin resistance. Treatment with some beta-blockers or high-dose diuretics may be associated with impairment in insulin sensitivity,

- Principal Hypertension Treatment
 1. Treat to BP <140/90 mmHg or BP < 130/80 mmHg in patients with diabetes or chronic kidney disease
 2. Majority of patients will require two medications to reach goal.
- Algorithm for Treatment of Hypertension

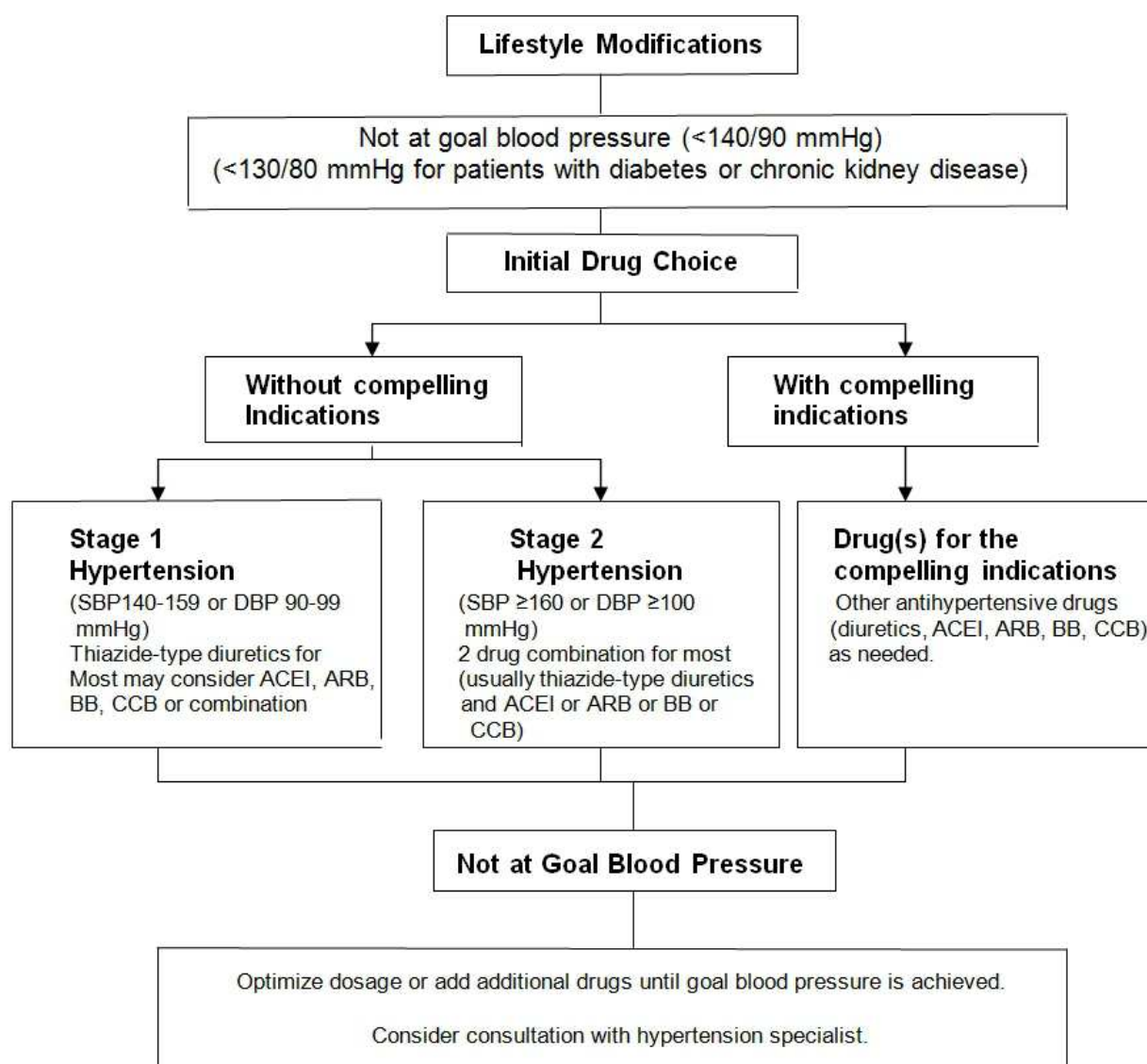


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whereas angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), renin inhibitors, and calcium channel blockers (CCBs) are ameliorative or neutral. The most pronounced improvements have been obtained with alpha1-blockers. In a recent study, data indicated that moxonidine, an imidazoline₁ receptor agonist, was effective in lowering blood pressure and improving insulin sensitivity in insulin-resistant patients. In populations at high risk of diabetes development, it may be justified to select drugs that improve insulin sensitivity when treating hypertension in insulin-resistant individuals [109]. The most important factor for choosing antihypertensive medications for hypertensive patients with diabetes is the prevention of the progression of renal damage [105, 110], which impacts drastically on mortality and morbidity in diabetic patients. Experience from clinical trials suggests that drugs that target the RAAS may have metabolic advantages over drugs such as beta-blockers and diuretics, but this conclusion has not been proved definitively. The number of antihypertensive medications needed for blood pressure control in patients with diabetes is largely dependent on the estimated glomerular filtration rate (renal function) rather than hyperglycemia control [110].

5.1 Angiotensin-Converting Enzyme inhibitors (ACE inhibitors)

The stimulation of the RAAS is a key factor in the development of hypertension in obesity. Pharmacological blockade of the RAAS not only improve blood pressure, but also has a beneficial effect on inflammation, oxidative stress, insulin sensitivity, glucose homeostasis, and resultant renal and cardio-protection. Several strategies are available for RAAS blockade, including angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blocker (ARBs), renin inhibitors (Aliskiren) and mineralocorticoid-receptor blockers, which have been proven in the clinical studies to result in improvements in cardiovascular disease and chronic kidney disease outcomes. Likewise, while hypertension in obesity, metabolic syndrome or type 2 diabetes, benefits from therapeutic lifestyle change, recently, clinical and epidemiological studies have shown that ACE inhibitors and ARBs are highly efficacious, persistent and well-tolerated antihypertensive agents, due to their cardio-and renal-protective benefits [58, 66, 67]. Moreover they have further beneficial effects in preventing complications of obesity and diabetes, such as progression of diabetic nephropathy, metabolic syndrome. Renin inhibitor may also exert favourable effects on insulin resistance [46]. In other words, the use of the RAAS blockers as initial treatment (both ARBs and ACEIs) in several cardiovascular, metabolic, obesity, and renal disorders (*i.e.* diabetes, ischemic heart disease, heart failure, and proteinuria) is now well-established.

The Heart Outcomes Prevention Evaluation (HOPE) study established that the significant effect of ACE inhibition (ramipril) on cardiovascular morbidity and mortality occurred through mechanisms beyond pure blood pressure control [58, 66]. Additionally, a recent analysis from the Blood Pressure Lowering Treatment Trialist's Collaboration showed that ARBs-based and ACE inhibitors -based treatment regimens were comparable in terms of the odds ratio for stroke and heart failure, independent of blood pressure reduction [111]. There is an emerging body of evidence suggesting that a combination approach to RAAS blockade with an ARB and an ACE inhibitor may further improve cardiovascular outcomes compared with mono-therapy with either agent alone [67]. In addition, some but not all clinical studies have shown that ACE inhibitors exert a favourable effect on insulin resistance [41, 49], lower plasma leptin, suppress the sympathetic nervous overactivity in obesity [11] and

provide renal protection especially in diabetic patients with renal injury [43]. The sympathetic inhibition, however, is much less than that achieved with centrally acting imidazoline anti-hypertensive agents. Therefore, ACE inhibitors have been recommended for use in special patients such as those with obesity, metabolic syndrome, diabetes, renal injury, or high risk of cardiovascular disease before the developments of ARBs [112]. The Irbesartan/HCTZ combination therapy and Blood Pressure Reductions in Diverse Patient Populations (INCLUSIVE) trial [113, 114] showed comparable antihypertensive efficacy and tolerability regardless of BMI or diabetes status.

5.2 Angiotensin II receptor blockers (ARBs)

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) program compared the efficacy of the angiotensin II receptor blocker (ARB) telmisartan, the angiotensin-converting enzyme (ACE) inhibitor ramipril, and combination therapy with telmisartan plus ramipril for reducing cardiovascular events [115, 116]. The ONTARGET trial involved 25,588 high-risk cardiovascular or diabetic patients with organ damage and compared the effectiveness of telmisartan with that of ramipril and showed that the two drugs were 'therapeutically equivalent'. Telmisartan is now the only ARB with clinical trial evidence of cardiovascular protection equivalent to that of ramipril, which is widely regarded as the 'reference' drug for RAAS blockade in patients at increased cardiovascular risk [116, 117]. The ONTARGET program consists of 2 randomized, double-blind, multicenter international trials: the principal trial, ONTARGET, and a parallel trial, Telmisartan Randomized Assessment Study in ACE-I Intolerant Patients with Cardiovascular Disease (TRANSCEND) [115]. Results of ONTARGET and the TRANSCEND have allowed us to better define the therapeutic approach in high-risk patients showing the favorable effects of either ramipril or telmisartan on blood pressure control and cardiovascular risk [115]. The results of the ONTARGET and TRANSCEND studies in patients with high risk cardiovascular disease as well as a number of recent meta-analyses of randomized trials comparing the efficacy and safety of ACE inhibitors to ARBs and their combination in patients with heart failure, hypertension, and chronic kidney disease focused attention on the RAAS.

Emerging data from experimental studies indicates a variety of beneficial effects of telmisartan [118]. In addition to blocking the angiotensin II type 1 receptor, telmisartan activates the peroxisome proliferator-activated receptor (PPAR)-gamma, a well-known target for treatment of the metabolic syndrome and diabetes. Few studies have analysed intra-class differences in ARBs with respect to anti-diabetic or metabolic effects. Makita *et al.* [119] examined a prospective randomized study comparing a PPAR gamma-activating ARB (telmisartan) with a non-activating ARB (candesartan), to delineate the effects on metabolic factors associated with cardiovascular disease in 153 hypertensive patient with glucose intolerance. Telmisartan decreased body weight while increasing serum adiponectin levels in hypertensive patients with glucose intolerance. Candesartan did not achieve similar improvements in these patients. Among ARBs, telmisartan may have a greater impact on obesity-related diseases.

5.3 Renin inhibitors

Recent pharmaceutical developments have shown that direct inhibition of renin results in decreased angiotensin I and II production and decreased urinary aldosterone excretion. Like

ACE inhibitors and ARBs, treatment with a direct renin inhibitor increases plasma renin concentration, but unlike the other RAAS inhibitors, treatment with a direct renin inhibitor decreases plasma renin activity. This unique combination of effects on the RAAS makes a direct renin inhibitor an attractive option to combine with other antihypertensive agents for the management of hypertension and its comorbidities [124]. Aliskiren/hydrochlorothiazide (HCTZ) therapy provides substantial BP reductions and may thus be a useful treatment option for older patients with stage 2 hypertension [125]. Clinical studies [126-128] including the ACTION study [125] have shown that combining aliskiren, with drugs representing each of the major classes of antihypertensive agents (thiazide diuretics, beta blockers, ACE inhibitors, ARBs, and CCBs) reduces blood pressure and improves markers of cardiovascular outcomes. Importantly, aliskiren had an ameliorative effect on insulin resistance in type 2 diabetic mice [46]. Persson *et al.* [129] investigated the effects of aliskiren on renal function and showed that aliskiren added to losartan reduced albuminuria and renal dysfunction and was well tolerated. In patients with type 2 diabetes, hypertension and albuminuria, aliskiren improved proteinuria [130]. Recently, Gao *et al.* [128] compared the efficacy between aliskiren and ARBs (losartan, valsartan and irbesartan) in 10 reports comprising 3,732 subjects and found that systolic and diastolic blood pressure reduction were similar. Results of several ongoing randomized clinical trials should provide additional insights into the potential of therapeutic combinations that include aliskiren to improve cardiovascular morbidity and mortality in patients with hypertension and related comorbidities. These studies have provided some further insight into the most effective strategy to prevent the adverse effects of RAAS activation. These insights may however need to be modified as the results of new strategies to block/inhibit the RAAS become available [131].

5.4 Calcium Channel Blockers (CCBs)

Calcium channel blockers (CCBs), especially newer long-acting dihydropyridines, may provide favourable metabolic effects by improving insulin sensitivity [49, 132, 133] and dampening the RAAS and sympathetic nervous activation in diabetes patients [47-49].

ACCOMPLISH (The Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension) trial was designed in order to evaluate the indications for CCBs [108, 132-135]. The ACCOMPLISH study compares the cardiovascular outcomes between combination of ACE inhibitor (benazepril)/CCB (amlodipine) and ACE inhibitor (benazepril)/diuretic (hydrochlorothiazide, HCTZ) therapy in patients with hypertension and high risk of cardiovascular events. The primary end point of cardiovascular morbidity and mortality was reduced by 20% in the benazepril/CCB arm and was superior to benazepril/HCTZ during the 30 months-follow-up. For 2,842 diabetic patients at very high risk given previous cardiovascular or stroke events, benazepril/CCB had significantly lower prevalence of albuminuria or microalbuminuria compared to benazepril/HCTZ [108]. In the whole cohort, there were less coronary events including acute coronary events and revascularization in the group with the benazepril/CCB. Side effects were generally more frequent with CCB than with the HCTZ combinations. Furthermore, the ACCOMPLISH study also showed that benazepril/CCB demonstrated a marked ameliorative effect on serum creatinine and end-stage renal disease than benazepril/HCTZ [135]. Therefore, the ACCOMPLISH study provided evidence indicating that ACEI/CCB combinations are more effective in selected high-risk patients than are ACEI/HCTZ

combinations [108, 132-135]. The AMANDHA Study [136] compared the effects on albuminuria between manidipine and amlodipine, as an additional medication on RAAS blockers. Both manidipine and amlodipine decreased blood pressure values to a similar extent. Urinary albumin excretion was reduced by 65.5% with manidipine versus 20% with amlodipine ($p < 0.01$) at 6 months and 62.7 versus 16.6% ($p < 0.01$) at 18 months. Thus, the addition of manidipine, but not amlodipine, resulted in a large reduction in the urinary albumin excretion rate despite similar blood pressure reductions [136].

Wiener *et al.* [137] showed that a combined therapy with an ACE inhibitor (benazepril) and a CCB (amlodipine) over 12 weeks had additive benefits on large-vessel compliance at similar levels of blood pressure lowering, compared with monotherapy with an ACE inhibitor (enalapril) in hypertensive patients with type 2 diabetes (52% vs. 32%, $P < 0.05$) [137]. In addition, sub-studies to The International Nifedipine GITS study, Intervention as a Goal in Hypertension Treatment (INSIGHT), showed that nifedipine GITS was significantly more effective at preventing an increase in intima-media thickness in the carotid artery and significantly slowed the progression of coronary calcification, compared with diuretics, oamilozide, which are frequently observed in diabetes and atherosclerotic c patients [138]. The results from INSIGHT support incorporating nifedipine GITS in the management of high-risk hypertensive patients to prevent atherosclerosis-related illness and death [138]. These observations suggest CCBs has an ameliorative effects on atherosclerotic damage.

Interestingly, in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, the risk of new-onset diabetes was reported to be 23% lower among patients initiating therapy with valsartan versus amlodipine [139]. Unadjusted absolute risks of diabetes were 21.4 (95% confidence interval (CI) 18.9-24.3) and 26.3 (95% CI 24.3-28.3) per 1000 patient-years for valsartan and amlodipine, respectively; the corresponding relative risk (RR) for valsartan was 0.82 (95% CI 0.70-0.94). The meta-analysis including 1,721 trials and 99,006 patients showed that CCBs were associated with a reduced incidence of new-onset type 2 diabetes (odds ratio 0.81; 95% confidence interval [CI] 0.73-0.90; $p = 0.0001$) compared with diuretic or beta-blocker therapy [140]. The reduction in new-onset type 2 diabetes was maintained when CCB were compared to only thiazide diuretics (OR 0.86; 95% CI 0.75-0.99; $p = 0.0346$). Thus, CCBs may have benefits for treatments for hypertension in type 2 diabetes due to an ameliorative effect on insulin resistance and reductions in new-onset of type 2 diabetes.

5.5 Imidazoline-receptor agonists (moxonidine)

Class differences in the effects of antihypertensive agents on metabolic indices may therefore be an important consideration when choosing treatment for patients who exhibit these characteristics [109]. Moxonidine, which selectively targets imidazoline type-1 receptors in the sympathetic vasomotor centres of the rostral-ventrolateral medulla, is an effective antihypertensive and has been reported to exert favourable metabolic effects in preclinical and clinical studies [141]. In obese hypertensive rats, chronic, but not acute, moxonidine treatment partially restored insulin sensitivity [142]. Moxonidine reduced blood pressure associated with insulin sensitivity in obese hypertensive patients [143]. Moreover, although moxonidine and amlodipine were associated with comparable reductions in blood pressure, only moxonidine significantly decreased sympathetic nervous activity, improved insulin resistance and reduced plasma leptin levels [144]. A small dosage of moxonidine

was effective to lowering blood pressure when it was used as a combination therapy with low-dose hydrochlorothiazides in hypertension with type 2 diabetes [145].

The MARRIAGE study (Moxonidine And Ramipril Regarding Insulin And Glucose Evaluation) has extended these preliminary observations by comparing the effects of moxonidine and the ACE inhibitor ramipril--and the combination of both drugs--on metabolic and haemodynamic parameters in patients with hypertension and impaired fasting glycaemia [146].

Both moxonidine and rilmenidine, were shown to exert beneficial effects, not only on blood pressure, but also lipid (reducing free fatty acids, triglycerides) [147, 148] and carbohydrate metabolism (improving glucose tolerance), and neurohormonal parameters such as plasma levels of norepinephrine, leptin, BNP, and ANP [149].

Moxonidine and rimenidine activates I_1 receptors in the RVLM, reducing the activity of the sympathetic nervous system [150, 151]. These I_1 -agonists have been shown to produce pronounced and long-lasting BP reduction in different animal models of hypertension, including the spontaneously hypertensive rats [152, 153]. Blood pressure reduction with moxonidine is usually accompanied by a reduction in heart rate which, however, is of shorter duration and lesser magnitude compared to the blood pressure reduction. Chronic administration of moxonidine to SHRs causes normalization of the heart and kidney damage (myocardial fibrosis, capillarization, regressive changes in myocytes, ventricular arrhythmia, left ventricular hypertrophy and renal glomerulosclerosis) in parallel with the reduction of blood pressure [152, 153]. Direct injection of moxonidine into the vertebral artery of cats elicits a more pronounced fall in blood pressure compared with intravenous injection of an equivalent dose, indicating the centrally origins of the antihypertensive effects [153]. In addition, drugs of this class appear to have the capacity to favorably modify insulin sensitivity, which has particular relevance in the treatment of hypertensive diabetic patients and obese hypertensive patients who may be insulin resistant. In the hypertension accompanying maturity onset diabetes and obesity, with recent recommendations from advisory bodies setting lower BP goals, and with these lower targets often being reached only with combinations of antihypertensive agents, it is advisable that all drugs used in combination therapy exert a favorable, or at least a neutral effect on insulin resistance .

Sharma *et al.* [154] showed the efficacy of moxonidine in treating hypertension in those with metabolic syndrome or obesity. A post-marketing surveillance study (CAMUS) involving 772 obese hypertensive patients with hypertension with and without the metabolic syndrome was conducted in Germany. Approximately 50% of subjects had metabolic syndrome and patients were treated with moxonidine and followed for 8 weeks. Reductions in BP were similar between subjects with and without the metabolic syndrome (both from 168/97 to 141/83 mmHg), but the BP reduction was particularly pronounced in patients with severe hypertension at baseline. The response rate (diastolic blood pressure $<$ or $=$ 90 mmHg or reduction $>$ or $=$ 10 mmHg) of antihypertensive treatment with moxonidine was also similar (94.0% for all patients versus 93.8% for patients with metabolic syndrome). After 8 weeks of treatment, patients achieved a mean weight loss of 1.4 kg, which was not surprisingly, particularly pronounced in obese patients. Moxonidine effectively reduced blood pressure in patients with the metabolic syndrome while simultaneously reducing body weight in obese patients.

In a study examining 77 obese hypertensive patients, Haenni *et al.* [155] used the hyperinsulinemia euglycemic glucose clamp technique and observed that treatment with

moxonidine for 8-9 weeks significantly improved insulin sensitivity in insulin-resistant obese hypertensive patients, but not in insulin-sensitive obese hypertensive patients. Sanjuliani *et al.* [144] compared the responses of blood pressure, sympathetic nerve activity and plasma levels of insulin and leptin to moxonidine and amlodipine treatment over a 24-week period. Blood pressure reductions were of similar magnitude between both treatments. Moxonidine significantly reduced arterial plasma epinephrine and norepinephrine concentrations, orthostatic venous plasma norepinephrine and plasma insulin and leptin levels 120 minutes subsequent to an oral glucose loading, whereas amlodipine did not change any of those parameters. This study clearly demonstrated a comparable reduction in blood pressure with both antihypertensive drugs, but the neurohormonal and metabolic effects were different between the antihypertensive drugs.

5.6 Low dose diuretics

Low-dose of diuretics as a first agent in treatment of patients with hypertension and diabetes is well documented and widely recommended [156-160]. This treatment has beneficial effects on both morbidity and mortality while, previous general concern on the negative impact of diuretics on the different lipid parameters and metabolic effects appear not justified as, all long-term studies with low-dose diuretics have not been shown to affect lipid and glucose profiles in a negative way [161-163]. Moreover, in studies of a year or more duration, diuretics have been shown to reduce cardiovascular risk [145, 164-166]. Very recently, it was reported that Chlorthalidone reduced cardiovascular events more than Hydrochlorothiazide, suggesting that Chlorthalidone may be the preferred thiazide-type diuretics for hypertension in patients at a high risk of cardiovascular risk such as in diabetic or obese patients [167].

5.7 Combination therapies

The clinical combination of hypertension and diabetes carries a particular poor diagnosis. Achievement of target blood pressure (<130/80 mmHg) in this patient category is crucial in decreasing premature morbidity and mortality. Thus, management of subjects with type 2 diabetes and associated hypertension needs to be early and aggressive, and must utilize a global approach. Now, especially for hypertensive patients with diabetes and obesity, multiple-medications are common [168].

6. Conclusions

Hypertension and type 2 diabetes are frequently associated with obesity. Life style modification with diet and exercise remains the initial treatment. Many subjects, however, fail to normalize/lose body weight, to maintain their weight loss, to control hyperglycemia, or to normalize blood pressure. Although diabetes mellitus is associated with increased risk of death and cardiovascular or renal events, much of this excess risk is attributable to coexistent hypertension.

Several large cohort trials have demonstrated that tight control of blood pressure significantly reduces cardiovascular morbidity and mortality and cardio-and renal complications in hypertensive patients with diabetes [101-103]. Based on these findings, contemporary treatment guidelines recommend a target systolic blood pressure/diastolic blood pressure of <130/80 mmHg for patients with diabetes, however, evidence shows that

most hypertensive patients with diabetes are very resistant to controlling hypertension and frequently require two or more types of antihypertensive medications to achieve blood pressure goals [103, 110].

Class differences in the effects of antihypertensive medications on metabolic indices and renal protective effects may therefore be an important consideration when choosing treatment for patients who exhibit these characteristics. Hypertension in type 2 diabetes is characterized as insulin resistance, which is associated with cardiovascular morbidity and mortality, and cardiac- and renal complications. Another important factor for choosing antihypertensive medications for hypertensive patients with diabetes is the prevention of the progression of renal damage, which impacts the mortality and morbidity in diabetic patients. While antihypertensive agents such as beta-adrenoceptor antagonists may worsen insulin resistance and impair glucose tolerance, ACE inhibitors or ARBs exert positive metabolic effects and renoprotection. Experience from clinical trials suggests the renal protective drugs that target the RAAS and CCBs and beneficial.

This article provides a synthesis of current findings with non-pharmacological and pharmacological treatments for hypertension in type 2 diabetes. Treatment of hypertension in type 2 diabetes is important with regards to the prevention of cardiovascular complications. To this stage, the preferred antihypertensive drug classes are somewhat uncertain, and disputed, however, smaller dosage of each class of drugs might lead less side events. Currently a combination therapy with 2 or more different classes of antihypertensive drugs is recommended [1, 4, 168]. Use of ACEIs and ARBs as the initial treatment in hypertension in type 2 diabetes is usually advocated as these agents exert favourable effects on insulin sensitivity and provide renal protection. A strong case for wider use of CCBs and the imidazoline drugs (moxonidine, rilmenidine) can also be made

There are many aspects of the pathogenesis, prevention and treatment of type 2 diabetes that still need to be uncovered before a complete strategy to reduce the ongoing epidemic and burden of type 2 diabetes may be offered.

7. References

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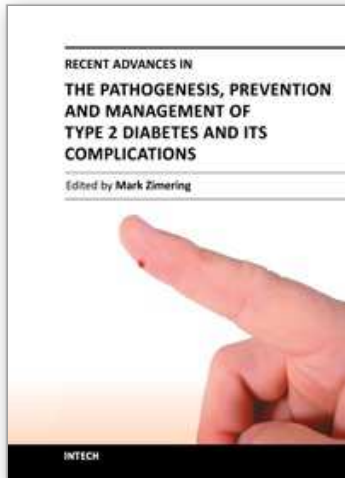
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Type 2 diabetes “œmellitus” affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

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