An In-Depth Study Of Prevalence Of New Onset Type 2 Diabetes Consequent To Use Of Various Anti-Hypertensive Drug Classes

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Abstract
A temporal relation exists between hypertension and diabetes, characterised by presence of several common risk factors. Apart from the causal commonality existing between the two, another aspect that relates the two is the use of antihypertensive drugs (AHDs). Population based data exists in number that shows varied levels of influence of various different classes of AHDs on carbohydrate metabolism, insulin resistance and subsequent risk to develop diabetes. But on the other hand, there are potential limitations that limit the representativeness of these data to population across borders, race, and ethnicity. Severity of illness, restricting characteristics of the included population, differences in prescription and practice patterns, and cost-utility differences, family history of diabetes, lifestyle habits, genetic factors, and fasting insulin and blood glucose levels measurement practices, all may highly influence the risk of diabetes development and all of these may not have been completely controlled in these studies. No AHD drug class has been evaluated in a placebo-controlled trial with diabetes incidence as a blinded, predefined primary endpoint. Also, there are chances that a population which has high baseline risk of developing diabetes may have been directed more to some specific high diabetes risk anti-hypertensive drug classes more often than the rest. Also, alpha-blocker drugs seem to have a significant protection to diabetes. Currently these are not used as first-cut therapy and also not as mono-therapy. And due to the fact that these drugs appear late in the algorithmic arrangements of AHDs, chances are that the added risk to the development of diabetes seen with polypharmacy use (2 or more) may not have emerged from their use in these combinations. As most of other AHD therapies increase the risk of developing diabetes, it will be important to address their independent effect on the development of diabetes by suitably controlled randomized trials targeted at suitable population. Also, their use and benefit in polypharmacy with 3 or more drugs should also be looked into.

BACKGROUND
Diabetes is an epidemic disease characterised by the human body’s inability to sufficiently use or sufficiently produce insulin. The disease can now be identified at almost all the nook and corners of globe with ever increasing proportions for morbidity, mortality, and healthcare costs and all this is expected to further increase in varying proportions [in the next coming decades].

Hypertension and diabetes are complex conditions, and are often seen to occur concurrently, mainly due to several common baseline factors, including dietary fat, physical inactivity, and upper body obesity etc. An important study conducted in 420 treatment-naive non-diabetic hypertensive individuals concluded to have up to 31% of these individuals as insulin resistant. Other metabolic derangements such as increased serum triglycerides, abdominal obesity, low HDL, and increased serum uric acid were also seen in 50, 50, 48, and 20 percentages of these individuals. [9] This could help us to understand that controlling metabolic risk factors alone may not be sufficient to limit or prevent the development of new diabetes.

The role of antihypertensive drugs (AHD) in carbohydrate metabolism and in the subsequent development or potentiation of diabetes has remained an unfailling clinical interest. The evidence for potential correlation can be deduced from several population based studies. For example, a long-term prospective study showed a several fold difference in the incidence of diabetes between treated hypertensive and non-treated normotensive men that was suspected to be as a consequence of treatment [10].

Furthermore, hypertension [11] and tachycardia [12] increases the risk by 2-4 times for the development of type 2 diabetes. Another study with 8 years of follow up called the “General
Practice Hypertension Study”, hypertensive men concluded to have 2.3-2.7 increased risk to develop diabetes compared to their age-matched normotensive control subjects [4]. Further evidence can be deduced from several studies such as population-based “San Antonio Heart Study” [5] and a 10-year “Uppsala longitudinal study of men” [6].

The evidence also exists that the treatment with any type of AHD medication, such as diuretic, beta-blocker, or hydralazine, at follow-up gives about 1.7 increased risks to develop diabetes independent of other risk factors [7]. However, conflicting data also exists [8].

The above studies suggest that the metabolic variables and AHD therapy may have been interlinked and could be detrimental in patients independent of other risk factors [9]. The present study compares major classes of AHD medications and their effects on new onset diabetes and blood glucose levels.

Figure 1

Pearls

AHD AND NEW ONSET DIABETES

RELATION BETWEEN AHD THERAPIES AND NEW-ONSET DIABETES AS A PRIMARY OBJECTIVE

A case-control [10] and a cohort [11] study have evaluated the relationship between different classes of AHD medications and the development of diabetes as their primary objective. They are described in details in the relevant sections below.

DIURETICS

Diuretic class of drugs include thiazide diuretics, loop diuretics, and potassium sparing diuretics. They are mainly the first-line treatment in most uncomplicated hypertensive individuals. They are also widely investigated and advocated for causing reductions in stroke, congestive heart failure, myocardial infarction, and other cardiovascular events [12].

Both kinds of results against diuretic and in favour of diuretics have been observed and will be discussed separately in this section.

Results against Diuretics: Cholesterol, mainly LDL, and triglyceride levels are known to rise with thiazides and related diuretics in susceptible patients as seen in a meta-analysis investigating effects of AHD medications on serum lipids which came with the conclusion that diuretics led to relative increases in cholesterol levels (0.13 mmol/L) and this increase was greater with higher doses and worse in Blacks than in non-Blacks [13].

In another “Systolic Hypertension in the Elderly” (SHEP) trial conducted in elderly showed that the metabolic changes are apparent with AHD medications during the 3-year timeframe, for example fasting glucose (+3.6 mg/dl), total cholesterol (+3.5 mg/dl), HDL cholesterol (-0.77 mg/dl), and triglycerides (+17 mg/dl) [14]. Also, new-onset diabetes was seen to occur more frequently in the study group compared to the placebo group (8.6% and 7.5%) respectively.

Similar results such as an increased glucose levels after 10 weeks (5 mg/dl), [15] 1 year (7 mg/dl), [16] and 2 years of thiazide therapy (9 mg/dl) are observed in other trials [17,18]. The evidence on the effect of thiazides on glycemic changes is also available from various case reports published on the subject [19,20].

Previous studies report both significant [21,22] and nonsignificant [23,24] associations between thiazides and new-onset diabetes. In a longitudinal study conducted in naïve hypertensive patients, 53.5% of patients treated with diuretic (mostly thiazide diuretic) developed diabetes compared to 30.4% of those in whom diabetes did not develop (p=0.002) [25]. The most important limitation of the study was the method of therapy assignment, after a median of 3-year follow-up; study participants were asked about their most frequently used anti-hypertensive therapy and were assigned to these therapies in a non-mutually exclusive fashion.

Two studies with new-onset diabetes as their primary objective did not find a significant increase in the risk of diabetes with thiazide diuretics [26,27]. Also, it is observed that the metabolic adverse effects associated with thiazide diuretics are generally infrequent and apparent only at high doses. Glucose intolerance is most marked among those in whom serum potassium decreases, [28] potassium supplementation may thus help prevent the development of diabetes in thiazide-treated patients [29].
A small study concluded that thiazide diuretic (chlorthalidone, 25mg/day) may possibly induce hyperglycemia and hyperinsulinemia and was associated with insulin resistance, especially in subjects who became hypokalemic [3].

Results in favour of Diuretics: A population-based observational study (n=2295) was conducted in hypertensive (n=2295) individuals and non-hypertensive individuals (n=2280) to investigate the development of new-onset diabetes. The study population was sub divided into two groups those taking diuretics and those not taking this drug, reported that after an average eight years of follow-up, there was only a marginally increased incidence of diabetes among individuals on diuretics as compared to those not on this treatment, and the difference was not considered to be statistically significant (5.83 vs. 4.79 and 6.40 vs. 5.53 per 1,000 men and women, respectively) [7].

Further evidence can be deduced from a case control study where no difference in risk to the development of diabetes was found between thiazide diuretics and other AHD therapies (ace inhibitors, central alpha2-agonists, peripherally acting anti-adrenergic agents, beta-blockers, calcium antagonists, and vasodilators). [14]

**Figure 2**

**Pearls**

**BETA-BLOCKERS (BB)**

Patients treated with beta-blockers are reported to have an increased risk for impaired glucose tolerance, decreased HDL, increased total cholesterol, and triglycerides, and to lesser extent on serum lipids [25]. Further evidence can be obtained from three small randomized trials which compared the metabolic effects of a beta-blocker (atenolol) to an alpha1-adrenergic blocker (doxazosin), [35] a calcium antagonist (nifedipine), [36] and another beta-blocker (metoprolol) were found and will be discussed here. [37]

In first study which compared atenolol to doxazosin, patients treated with atenolol tended to have decreased insulin sensitivity after 3 months of therapy, however, the effect was considered to be statistically non-significant, but the statistical significance may be limited by the fact the study was quite small in number of study population (n=29). Also, a subgroup of patients treated with doxazosin (n=18) were followed-up for 12 months, and showed that the insulin sensitivity, basal and late insulin response to glucose tolerance tests increased significantly. These beneficial metabolic effects were more pronounced among “high-risk” patients those with high triglycerides, low HDL level, and high fasting blood glucose.

In the second trial, insulin resistance appeared to increase in patients treated with atenolol and decrease among those treated with nifedipine during the 4-month treatment of 24 anti-hypertensive patients.

In the third small randomized trial of 60 hypertensive patients, insulin resistance decreased among patients taking both metoprolol and atenolol. Glucose uptake decreased from 5.6 to 4.5 mg/kg/min among patients taking metoprolol and from 5.6 to 4.9 mg/kg/min among patients taking atenolol during the four-month study period when measured by euglycemic hyperinsulinemic clamp technique. In addition, both medications increased fasting plasma insulin and blood glucose concentrations as well as hemoglobin A1C concentration by small amounts. So, this approximately 15-20% decrease in the insulin sensitivity with metoprolol and atenolol seem to be important even in this small study with short duration.

Finally, another observational study (N=12,550), middle-aged cohort (between 45 to 64 years old) showed that the risk of diabetes was associated with beta-blockers, but not with diuretics [13]. The relative hazard to develop diabetes was 0.91 (95% CI: 0.73-1.13) for patients taking thiazide diuretics, while it was 1.28 (95% CI: 1.04-1.57) for those on beta-blockers. Major limitations however, in this study were lack of control for important aspects of AHD therapy, such as medication compliance and duration of therapy as well as medication/dose changes. Furthermore, it has been argued that the dose of diuretics in this investigation was lower than in earlier studies [1].

Overall, it appears that patients taking beta-blockers consistently experience negative effects on carbohydrate metabolism, which increases their risk to develop diabetes. The effect appeared to be most pronounced among high-risk patients, who already possess some factors of the metabolic syndrome.
THE EFFECT OF COMBINATION OF DIURETICS AND BETABLOCKERS ON GLUCOSE METABOLISM

Some trials have investigated the combined effect of thiazide diuretics and beta-blockers on glucose metabolism. For example, in a Finnish prospective population-based study, hypertensive elderly patients treated with thiazide diuretics, beta-blockers, or both had 1.88 increased risks to develop type 2 diabetes compared to their normotensive counterparts during the 3.5-year study period \[11\]. Using hypertensive patients not treated with diuretics/beta-blockers as a comparison group, the excess risk was 1.56. After adjustment for age, gender, BMI, waist-to-hip ratio, and fasting glucose and insulin levels, the relative risk was 1.56 for those taking diuretics/beta-blockers. And even after further adjustment for 2-h glucose and insulin levels, the incidence of type 2 diabetes did not differ between the two groups.

Very similar findings were reported in a population-based “San Antonio Heart Study”, which included Mexican Americans and non-Hispanic White Americans and concluded that hypertensive patients remained at increased risk to develop impaired glucose tolerance (IGT), even after controlling for the other risk factors with an odds ratio of 1.87 (95% CI: 1.08-3.22) \[8\].

A 10-year population-based “Uppsala study of hypertensive men” showed that treatment with beta-blocker, diuretic, or hydralazine was an independent risk factor for new-onset diabetes \[10\] even after controlling for glucose and insulin levels, insulin increment from baseline, BMI, and systolic blood pressure.

Another, 15-year Swedish trial called “The Primary Prevention Trial” of 686 middle-aged hypertensive men showed a relative risk for developing diabetes was significantly higher among patients taking non-selective beta-blockers such as alpranolol compared to those taking thiazide diuretics such as chlorthalidone, hydrochlorothiazide. This relative risk during the 15-year study period was 2.09 (95% CI: 1.32-3.29) for patients taking beta-blockers and 0.88 (95% CI: 0.58-1.32) for patients on diuretics \[38\]. However, many patients in the thiazide diuretic group also received potassium supplementation, which may have been the reason for the lower risk of diabetes in this group \[33\].

In conclusion, treatment with beta-blockers may trigger the development of diabetes more easily in predisposed populations characterized by higher blood pressure levels as a consequence of insulin resistance.

CALCIUM ANTAGONISTS

They are potent vasodilators and reduce blood pressure by reducing the total peripheral resistance. The non-dihydropyridine members of this class such as verapamil have negative inotropic effect on myocardial contractility. Dihydropyridine calcium agonists such as amlodipine, nifedipine are more potent vasodilators and have less inotropic effect. Long-acting calcium blockers are preferred in the treatment of hypertension \[41\]. Very few metabolic effects have been associated with calcium blocker therapy and they do not appear to be clinically important, however, opposite results also appear \[14, 42\].

ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)

ACEIs act by preventing the production of angiotensin II and, through a separate mechanism, inhibit the degradation of bradykinin \[43\]. Bradykinin is a vasodilator and its increased production on the one hand, results in further decrease in blood pressure and on the other hand gives added side-effects, primarily the dry cough.

Several small trials have also shown positive effects on carbohydrate metabolism in hypertensive individuals, although conflicting results also exist. Variability of the results may be due to several factors such as differences within the class of ACEIs, variations regarding the risk of diabetes in the study populations, or type II errors inherent in small investigations. In short-term, randomized studies,
treatment with captopril [44] and enalapril [45] resulted in improved insulin sensitivity; however, both positive [46] and neutral [47] effects have been reported with lisinopril therapy. Several large long-term clinical trials also seem to support lower risks among hypertensive patients treated with ACEIs. A longer duration study comparing the effect of trandolapril and atenolol found reduced insulin sensitivity with atenolol but no change with trandolapril therapy [48].

“The Captopril Prevention Project (CAPPP)” which used ACEIs and conventional therapy using diuretics and beta-blockers and investigated cardiovascular morbidity and mortality in patients with hypertension reported that the new-onset diabetes was lower in the captopril group (ACEI) than in the conventional therapy group, with relative risk (RR) of 0.86 and absolute risk reduction (ARR) of 0.01. This benefit was achieved, despite the fact that patients in the captopril group had higher baseline blood pressure (both systolic and diastolic). The study concluded that the benefit to prevent new-onset diabetes was above and beyond the blood pressure normalization effect [49].

The “Heart Outcomes Prevention Evaluation (HOPE) trial” also found similar results as to the CAPPP findings among elderly individuals with high cardiovascular risk [50]. Fewer cases of new-onset diabetes occurred among patients randomized to take ramipril compared to patients in the placebo group during the 4.5-year follow-up. The relative risk and absolute risk reduction showed an even more positive beneficial effect than reported in the CAPPP trial—RR (0.67) and ARR (0.02). Significance in the positive results could be that the risk reduction occurred despite the similar baseline diabetes risk factors in the comparison groups. However, new-onset diabetes was neither a primary nor a secondary outcome of the study.

Enalapril (ACEI) reduced the incidence of diabetes to an even greater extent in a retrospective analysis of patients with asymptomatic left ventricular dysfunction who were enrolled in the “Studies of Left Ventricular Dysfunction (SOLVD)”. Enalapril therapy resulted in a hazard ratio of 0.22 (95% CI: 0.10-0.46) to develop diabetes during the almost 3-year follow-up period [51]. This study adds support to previous studies, as the incidence of diabetes was determined by using strict biochemical definition (= 126 mg/dl fasting plasma glucose on at least 2 visits). The positive effect of enalapril was even more striking among pre-diabetic patients with impaired fasting blood glucose. However, it has also been argued that whether these results were actually due to the protective effect of ACEIs or the adverse effect of beta-blockers. The evidence may lie in another large prospective “Atherosclerosis Risk in Communities (ARIC) study” which reported higher incidence of diabetes (+28%) with beta-blockers (relative hazard of 1.28). Patients in the ARIC study who were taking beta-blockers had a 28 percent higher risk of subsequent diabetes (relative hazard of 1.28).

A meta-analysis investigating metabolic side effects of ACEIs, reported that the ACEIs reduce triglycerides (-0.07 mmol/L), and, in patients with diabetes, total cholesterol (-0.22 mmol/L) [52].

Figure 5
Pearls

Several small trials show relatively lesser effect of ACEIs on hypertensive patients’ carbohydrate metabolism, although results are not uniform. Similar results seen in large blinded trials also showed a reduced incidence of diabetes associated with ACE therapy [53].

One long-term study concluded with a reduced insulin sensitivity with atenolol as compared to no change with trandolapril. In a case-control investigation of medicare recipients, patients treated with ACEIs were at increased risk to develop diabetes. However, a large cohort study did not find such an association. [54]

In summary, existing evidence suggests neutral to beneficial effect.

ANGIOTENSIN II RECEPTOR BLOCKERS (ARB)

Literature evidence supports similar benefits to ACEIs regarding the effect of ARBs on carbohydrate metabolism. A 5-year “Losartan Intervention for Endpoint Reduction study (LIFE)” (n=10,000) conducted in individuals with essential hypertension and an average of 67 years of age (age range 55-80 years), who received either losartan 50mg or atenolol 50mg, showed that the losartan treated patients had a lower incidence of diabetes (13.0/1,000 patient years) as compared to those in the atenolol group (17.4/1,000). The adjusted odds ratio showed benefit to the losartan group with adjusted hazard ratio (95% CI) of 0.75 (0.63-0.88). [55]

In patients without clinically evident vascular disease also reported a similar protective effect associated with losartan [56]. These findings are comparable to those reported in the “HOPE” trial. However, the same questions as with ACEIs linger around with ARBs that whether these results are actually a “real reflection” of protective effect of ARBs or due to the known adverse effects with beta-blockers. Furthermore “Study on Cognition and Prognosis in the Elderly (SCOPE)” showed that candesartan was associated with a 20% relative reduction in the incidence of diabetes,
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but the reduction was not statistically significant. However, the reduction was not statistically significant.

**TRUE BENEFIT OR TRUE RISK**

The evidence exists that may help understand the “true risk potential of ACEIs or ARBs” and that may work for beta blockers lies in the potential of “over prescription” of beta-blockers as seen in “LIFE study” with a 25% risk reduction but beta-blockers were taken more frequently by patients in the placebo group compared to those in the candesartan group which may have confounded the obtained results.

**Figure 6**

**Pearls**

![Pearls](image)

**ALPHA BLOCKERS**

Consistent evidence suggests that points towards improved insulin sensitivity with these drugs and is presented in table below and discussed in part in section above however more appropriately controlled trials are needed to support the available evidence.

**Figure 7**

**Pearls**

![Pearls](image)

**POLYPHARMACY AND DIABETES RISK**

Also, polypharmacy may also increase the risk to develop diabetes, as seen in a case-control study. The odds ratio of developing diabetes was higher (OR of 1.76-1.93) when patients were treated intensively (i.e., polypharmacy including diuretics), compared to the baseline risk associated with AHD mono-therapy (OR of 1.40-1.77). Thus, it could be concluded that the polypharmacy may increase the risk of new-onset diabetes, although the magnitude of this increase likely depends on the components and the number of combination drugs.

**AHD THERAPIES AND CHANGE IN BLOOD GLUCOSE**

A 3-year, double-blind, placebo-controlled “Systolic Hypertension in the Elderly Program (SHEP) trial” was conducted in which hypertensive patients received thiazide (chlorthalidone) initially, and then a beta-blocker (atenolol) or central alpha2-agonist (reserpine), if blood pressure was not sufficiently controlled. This study concluded that those patients who were on thiazide diuretics showed a significant increase in fasting glucose levels (FBG) (by 3.6 mg/dL). However, the major limitation of this trial was that this effect may have been actually more than what is reported as FBG generally gives smaller variance as compared to random blood glucose values.

Another study called “The VA Cooperative Study Group Study on AHD Agents” reported larger increase in glucose levels following a 10-week and a one-year monotherapy with either beta-blocker (propranolol) or thiazide diuretic (hydrochlorothiazide). The study showed a significant increase in average plasma blood glucose values (by approximately 5 mg/dL) after 10-week and one-year of therapy with both drugs. The results from this study may also have been infected by the same reason given above that they also evaluated changes in fasting blood glucose rather than a random blood glucose, which limits the comparability.

In a double-blind randomized, placebo-controlled “European Working Party on high blood pressure in the elderly (EWPHE) Trial” in which patients received thiazide diuretic (with the addition of methyldopa in 30% of the subjects) concluded a smaller average fasting blood glucose increase than seen in above two trials (by 2.5 mg/dL). The major characteristic of this study was that upon follow up for one year no further increase in their blood glucose levels was found.

**DISCUSSION**

Firstly, it is important to note that no AHD drug class has been evaluated in a placebo-controlled trial with diabetes incidence as a blinded, predefined primary endpoint. Secondly, there is a difficulty to draw firm conclusions from the results of studies comparing two or more AHD agents because of the uncertainty whether the observed effect is a beneficial effect of one drug, or the detrimental effect of the other. Thirdly, there are chances that a population which has high baseline risk of developing diabetes may have been directed more to some specific high diabetes risk anti-hypertensive drug classes more often than the rest, could have played a role in the results. Fourthly, some results may have been limited by relatively short follow-up period and lack of adequate comparison groups or inconsistent definition of diagnosis of diabetes; and conflict with FBG or
RBG measurements. Fifthly, although the evidence may not be sufficient, alpha-blocker drugs seem to have a significant protection. Currently these are not used as first-cut therapy and also not as mono-therapy. And since chances are that majority of patients will eventually receive polypharmacy, these drugs may be added in the regular combination anti-hypertensive regimens, especially with diuretics. Also due to their ability to improve insulin sensitivity and as insulin resistance may be an antecedent of type 2 diabetes, it is expected that in the long-run these medications may play a role in the incidence of diabetes. And due to the fact that these drugs generally appear late in the algorithmic arrangement of the AHDs in the course of treatment, chances are that the added risk to the development of diabetes with polypharmacy use (2 or more) may not have emerged from their use in these combinations. As most of other AHD therapies increase the risk of developing diabetes, it will be important to address their independent effect on the development of diabetes by suitably controlled randomized trials targeted at suitable population. Also, their use and benefit in polypharmacy with 3 or more drugs should also be looked into.

CONCLUSIONS

To summarize, there is a certain relationship between hypertension and diabetes which is extremely complex and affected by many factors each surrounding insulin resistance. An increased risk of developing type 2 diabetes by using various AHD drug classes does exist, especially with ACEIs, CCBs, and diuretics. Finally, it is difficult to draw direct conclusions from the above discussed clinical trials. Blood glucose levels may increase naturally over time especially in individuals with baseline presence of other diabetes risk factors; on the other hand, it is quite evident that the amount of this blood glucose change may vary between those who do not receive any therapy to those who receive mono-, poly- (2+) or poly (3+) pharmacy.

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