Prevalence of insulin resistance among hypertensive patients undergoing antihypertensive therapy

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Abstract:

Background: Hypertensive patients undergoing antihypertensive therapy are more prone to insulin resistance (IR). Thus, it is essential to monitor its prevalence, metabolic consequences and to individualize antihypertensive therapy to negate its potential adverse effects. Therefore, the presented study assessed the prevalence of IR among hypertensive patients undergoing antihypertensive therapy.

Methodology: This prospective study involved 200 patients of either sex, diagnosed with essential hypertension, and undergoing treatment. Data regarding age, gender, medical history, body mass index (BMI), and waist circumference were collected. Laboratory investigations for fasting blood sugar levels, serum fasting insulin levels, lipid profile, and glycosylated hemoglobin were performed. Homeostatic model assessment of IR (HOMA IR) was calculated. Statistical analysis was performed by using R software (Version. 3.6.0).

Results: The prevalence of IR in hypertensive nondiabetic patients was 39%. The mean age and BMI of patients were 58.70 ± 16.64 year and 23.10 ± 2.57 kg/m², respectively. The mean fasting blood sugar levels were 108.24 ± 20.99 mg/dl. The mean HOMA IR levels were >2.8. IR was more in users of beta-blockers than in angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers, as a significant association was observed between the class of hypertensive drugs and presence of IR (P < 0.05). A significant association (P < 0.05) was observed between the duration of hypertension and IR indicated by HOMA IR >2.5 in patients on beta-blockers and on ACE inhibitors.

Conclusion: Antihypertensive drugs like beta-blockers decrease insulin sensitivity in hypertensive patients leading to increased prevalence of IR.

Keywords: Antihypertensive agents, Blood glucose, Hypertension, Insulin resistance

Introduction:

Hypertensive patients have a high insulin resistance (IR) prevalence and have a relatively high risk of Type 2 diabetes mellitus (DM) development. In comparison to normotensive patients, the patients of essential hypertension generally have higher postprandial and fasting insulin levels, regardless of body fat distribution or body mass index (BMI).[1] At least 50% of hypertensive patients are insulin resistant as per estimations, which is one basic abnormality in the pathogenesis of the cardiometabolic syndrome.[2] Antihypertensive medications have incongruent effects on insulin sensitivity in patients with essential hypertension.[2] In terms of long-term implications and increased risk of adverse outcomes, the antihypertensive medications of special concern are beta-blockers, and some angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs).[2] However, ARBs and ACEI have also shown beneficial metabolic effects on glucose homeostasis.[3]
Antihypertensive drugs have varying effects on metabolic factors and IR. Beta-adrenergic blockers, especially nonselective and higher-dose selective agents, have been implicated in altering glucose homeostasis, primarily through inhibition of pancreatic insulin secretion and promoting IR. Calcium channel blockers (CCBs), are generally considered metabolically neutral.[4] Few studies have attempted to investigate the prevalence and effect of antihypertensive drugs on insulin sensitivity in hypertensive patients before diabetes sets in.[5] Therefore, this study assessed the prevalence of IR among hypertensive patients undergoing antihypertensive therapy.

Methodology:
Study design
After obtaining approval from the institutional ethics committee (Approval no:KIMSDU/IEC-307/022/06/06/2018), this single-centred, hospital-based, prospective, cross-sectional, observational study was conducted in the Department of General Medicine at a private medical college in Karad (Maharashtra) over a period of 1 year (January 2019–December 2019). Informed consent was obtained from all the patients included in the study.

Selection criteria
Two hundred nondiabetic patients of either gender, aged ≥18 years, diagnosed with essential hypertension, and undergoing treatment for more than 2 years in the Department of General Medicine were included in the study. Patients diagnosed with DM (Type 1/ Type 2/secondary D. M.), secondary hypertension, hypothyroidism, hyperthyroidism, renal failure, and any malignancy were excluded from the study.

Data collection
Data regarding age, gender, medical history, and anthropometric measurements, namely BMI and waist circumference (WC) were collected for all the patients.

Lab investigation
Blood samples were collected from all the patients after 6–8 h of fasting and was tested for fasting blood sugar levels, serum fasting insulin levels, lipid profile, and glycosylated hemoglobin.

Homeostatic model assessment of IR (HOMA IR)[6] was calculated by using the following formula:[7]

\[
\text{HOMA IR} = \frac{\text{FSI} \times \text{FPG}}{405}
\]

Here, FSI: Fasting serum insulin (µU/ml); FPG: Fasting plasma glucose (mg/dl).
The HOMA IR of ≥2.5 was considered IR.[8]

Statistical analysis
Statistical analysis was performed by using R software (Version. 3.6.0). Data were recorded in Microsoft Excel and expressed as mean and standard deviation along with frequency and percentage. Qualitative variables were analysed using the Chi-square test of independence. Data were considered statistically significant when \( P \leq 0.05 \).

Results:
In the present study, there were 110 males (55%) and 90 females (45%). The prevalence of IR in hypertensive nondiabetic patients was 39%. Table 1 presents the demographic and clinical data.

| Variables       | Minimum value | Maximum value | Mean±SD |
|-----------------|---------------|---------------|---------|
| Age (years)     | 21            | 88            | 58.70±16.64 |
| BMI (kg/m²)     | 16.80         | 32.10         | 23.10±2.57  |
| BSL (F) (mg/dl) | 69            | 113           | 108.24±20.99 |
| Insulin (F) (µu/ml) | 0.50      | 20.50         | 7.55±4.14   |
| HOMA IR         | 0.09          | 8.63          | 2.84±1.84   |
| Duration of HTN (years) | 3 | 20 | 12.5±5.82 |
| Total cholesterol (mg/dl) | 132 | 220 | 181.49±15.34 |
| Triglycerides (mg/dl) | 31    | 179        | 94.01±20.45 |
| HDL (mg/dl)     | 20            | 84            | 64.35±10.65 |
| LDL (mg/dl)     | 78            | 142           | 95.25±13.96 |
| VLDL (mg/dl)    | 6             | 36            | 21.88±5.34  |

BMI: Body-mass index; BSL (F): Blood sugar level (fasting); HOMA IR: Homeostatic model assessment of insulin resistance; HTN: Hypertension; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein

Majority patients were old aged. Most of the patients were within a healthy weight range (8.5–24.9 kg/m2) and were suffering with hypertension for 12 years. The mean fasting blood sugar levels indicated considerable prediabetes condition. Further, the mean total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very LDL (VLDL) were in the normal range. However, the mean HOMA IR levels were above 2.8 indicating significant IR [Table 1].
IR was seen more in users of beta-blockers as compared to that in ACE inhibitors and CCBs. A significant association was observed between the class of hypertensive drugs and presence of IR (P < 0.05) [Table 2].

| Class           | Antihypertensive medication class | HOMA IR frequency n(%) >2.5 | >2.5 | Total | P<0.05* |
|-----------------|----------------------------------|------------------------------|------|-------|---------|
| A (ACE inhibitors) | 46 (71.88)                      | 18 (28.28)                   | 64 (100) | 0.003* |
| B (β blockers)   | 6 (30)                           | 14 (70)                      | 20 (100) |       |
| C (CCBs)        | 70 (60.35)                       | 46 (39.65)                   | 116 (100) |       |
| Total           | 142 (71)                         | 78 (29)                      | 200 (100) |       |

*Significant; Chi-square test. ACE: Angiotensin-converting enzyme; CCBs: Calcium channel blockers; HOMA IR: Homeostatic model assessment of insulin resistance

No significant association was observed between the duration of hypertension and presence of IR (P > 0.05) [Table 3].

| Class of Hypertensive Drugs | Hypertensive drug class | HOMA IR frequency n(%) >2.5 | >2.5 | Total | P<0.05* |
|-----------------------------|-------------------------|------------------------------|------|-------|---------|
| A (ACE inhibitors)          | 15 (86.33)              | 16 (69.77)                   | 31 (100) | 0.035* |
| 11-15                       | 16 (69.77)              | 3 (75)                      | 25 (100) | 0.00149* |
| 16-20                       | 5 (41.67)               | 7 (58.33)                   | 12 (100) |       |
| >20                         | 10 (90.99)              | 1 (9.09)                    | 11 (100) |       |
| Total                       | 46 (71.88)              | 18 (28.28)                  | 64 (100) |       |

| B (β blockers)              | 11 (91.67)              | 2 (8.33)                    | 12 (100) | 0.01149* |
| 11-15                       | 12 (100)                | 0 (0)                      | 12 (100) |       |
| 16-20                       | 2 (100)                 | 0 (0)                      | 2 (100) |       |
| >20                         | 2 (100)                 | 0 (0)                      | 2 (100) |       |
| Total                       | 6 (30)                  | 14 (70)                    | 20 (100) |       |

| C (CCBs)                    | 15 (75)                 | 5 (25)                     | 20 (100) | 0.2324 |
| 11-15                       | 15 (75)                 | 5 (25)                     | 20 (100) |       |
| 16-20                       | 15 (75)                 | 5 (25)                     | 20 (100) |       |
| >20                         | 4 (20)                  | 1 (5)                      | 5 (100) |       |
| Total                       | 30 (60.34)              | 18 (37.66)                 | 48 (100) |       |

*Significant; Chi-square test. ACE: Angiotensin-converting enzyme; HOMA IR: Homeostatic model assessment of insulin resistance; HTN: Hypertension

A significant association (P < 0.05) was observed between the duration of hypertension and IR indicated by HOMA IR >2.5 in patients on ACE inhibitors/ ARBs and on beta-blockers, especially in patients with a history of 11–15 years of hypertension (in case of Class A) and in patients with a history of <11 years of hypertension (in case of Class B) [Table 4]. However, no significant association (P > 0.05) was observed between Class C of hypertensive drugs with the occurrence of IR [Table 4].

**Discussion:**

The utilization of antihypertensive drugs in the treatment of hypertension has varied effects on glucose metabolism, leading to IR. Their use as hypertensives has been associated with the development of IR.

Therefore, this prospective study aimed at assessing the prevalence of IR among hypertensive patients undergoing antihypertensive therapy.

The prevalence of IR in hypertensive nondiabetic patients in the presented study was 39%. The estimates of prevalence provided by two previous studies regarding IR in patients with hypertension were 20% and 9%.[9,10] This difference could be attributed to different study races in the comparative studies.

In this prospective study, majority of the patients were old aged with male predominance. Most of the patients were within a healthy BMI and were suffering from hypertension for around 12 years. The mean fasting blood sugar levels indicated considerable prediabetes condition. Further, the mean total cholesterol, triglycerides, HDL, LDL, and VLDL were in the normal range. This is in accordance with the study conducted by Mancusi et al.[11] in which most of the patients were 50–60-year-old, with BMI 25 ± 2 and normal mean values for triglycerides, HDL, LDL, VLDL, and total cholesterol. In their study population, the prediabetes blood sugar levels. Further, the mean HOMA IR levels were >2.8 indicating significant IR. However, their study showed female predominance.[11] This difference could be attributed to the difference in study population from different study are in comparison to our study.

IR was seen more in patients using beta-blockers as antihypertensive medication. Further, beta-blockers had a greater number of patients with IR as compared to ACE inhibitors or CCBs. This is consistent with the results of previous studies which noted more IR in patients using beta-blockers as compared to other antihypertensive drugs.[1,12,13]

**Table 2: Association between insulin resistance homeostatic model assessment of insulin resistance and different antihypertensive medication classes**

| Class of Hypertensive Drugs | Antihypertensive medication class | HOMA IR frequency n(%) >2.5 | >2.5 | Total | P<0.05* |
|-----------------------------|----------------------------------|------------------------------|------|-------|---------|
| A (ACE inhibitors)          | 46 (71.88)                      | 18 (28.28)                   | 64 (100) | 0.003* |
| B (β blockers)              | 6 (30)                           | 14 (70)                      | 20 (100) |       |
| C (CCBs)                    | 70 (60.35)                       | 46 (39.65)                   | 116 (100) |       |
| Total                       | 142 (71)                         | 78 (29)                      | 200 (100) |       |

**Table 3: Association between insulin resistance homeostatic model assessment of insulin resistance and different antihypertensive medication classes**

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|-----------------------------|-------------------------|------------------------------|------|-------|---------|
| A (ACE inhibitors)          | 15 (86.33)              | 16 (69.77)                   | 31 (100) | 0.035* |
| 11-15                       | 16 (69.77)              | 3 (75)                      | 25 (100) | 0.00149* |
| 16-20                       | 5 (41.67)               | 7 (58.33)                   | 12 (100) |       |
| >20                         | 10 (90.99)              | 1 (9.09)                    | 11 (100) |       |
| Total                       | 46 (71.88)              | 18 (28.28)                  | 64 (100) |       |

| B (β blockers)              | 11 (91.67)              | 2 (8.33)                    | 12 (100) | 0.01149* |
| 11-15                       | 12 (100)                | 0 (0)                      | 12 (100) |       |
| 16-20                       | 2 (100)                 | 0 (0)                      | 2 (100) |       |
| >20                         | 2 (100)                 | 0 (0)                      | 2 (100) |       |
| Total                       | 6 (30)                  | 14 (70)                    | 20 (100) |       |

| C (CCBs)                    | 15 (75)                 | 5 (25)                     | 20 (100) | 0.2324 |
| 11-15                       | 15 (75)                 | 5 (25)                     | 20 (100) |       |
| 16-20                       | 15 (75)                 | 5 (25)                     | 20 (100) |       |
| >20                         | 4 (20)                  | 1 (5)                      | 5 (100) |       |
| Total                       | 30 (60.34)              | 18 (37.66)                 | 48 (100) |       |
During treatment with conventional \( \beta \)-blockers, unopposed \( \alpha_1 \)-activity causes vasoconstriction and decreased blood flow to muscles. This effect results in reduced insulin-stimulated glucose uptake, in other words, IR.[14] Treatment with \( \beta \)-blockers can also interfere with insulin secretion from pancreatic \( \beta \) cells. The \( \beta \)-blockers decrease the first phase of insulin secretion, possibly through an impairment of \( \beta_2 \)-mediated insulin release.[15]

A significant association was observed between the duration of hypertension and IR indicated by HOMA IR >2.5 in patients on ACE inhibitors and on beta-blockers, especially in patients with a history of 11–15 years of hypertension (in case of Class A) and in patients with a history of <11 years of hypertension (in case of Class B). Patients on CCBs did not show any significant association among duration of hypertension and IR. Huang et al.[16] also found a similar association in patients on beta-blockers among duration of hypertension and IR among increasing age group patients.[16] However, in contrast to our findings, a study done by Stump et al.[1] noted that, there probably is a modest class effect of ACE inhibitors that enhances insulin-mediated glucose disposal; the mechanism of this effect is likely to be a combination of increased muscle blood flow, local renin-angiotensin system blockade and elevated kinin levels.[1] Many studies have noted that ARBs have beneficial effects on glucose metabolism independent bradykinin mediated mechanism.[14]

This study has its own limitations. First, BMI was measured by using WC only. Second, the study was monocentric and hence we cannot generalize IR as a first line investigation in our resource limited nation. Further multicentric studies involving diverse ethnicity of population are warranted.

**Conclusion:**

Hypertensive patients, the antihypertensive agents, namely beta-blocker and ACE inhibitor, caused IR. The prevalence of IR in hypertensive nondiabetic patients was 39%. Further, beta-blocker had a greater number of patients with IR as compared to ACE inhibitors.

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