First Line Antihypertensive Drug Therapy and its Complications

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Abstract
Hypertension using β adrenergic antagonist and Diuretic as first line therapy is associated with risk of NIDDM due to weight gain, Attenuation of the beta receptor mediated release of insulin from pancreatic beta cell. Decreased blood flow through the microcirculation in skeletal muscle tissue leading to decreased insulin sensitivity and impair insulin stimulated uptake of glucose in peripheral tissues.

Keywords: Hypertension; β adrenergic antagonist; Diuretic; pancreatic beta cell; insulin

Introduction
Hypertension commonly defined as a sustained systolic blood pressure of 140 mm Hg or higher or a sustained diastolic blood pressure of 90 mm Hg, numerous studies have shown that untreated high blood pressure damages blood vessels, accelerates atherosclerosis and produces LVF Hypertrophy1. The antihypertensive drugs used in India are mainly Diuretics, β blocker, Calcium channel blocker and RAS Antagonists. The preferred first line treatment for majority of the patients was largely based on the findings of Antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT)2, although this is in line with the recommendations of latest report of JNC (7th) but recent reports have generated significant controversy about the safety of β-blockers and diuretics because both of these classes of drugs are associated with new onset of diabetes mellitus, dyslipidemia and weight gain in significant proportion of hypertensive patient population therefore we hereby review the An follow up recommendations of joint National committee on prevention, detection, evaluation and treatment of high blood pressure (JNC7)3 is given in table no 1.

First line antihypertensive drug therapy and risk of diabetes
Beta blocker
Beta –blockers are commonly used as first line agents for the treatment of essential hypertension. The most commonly used beta blockers in hypertension include Atenolol, Metoprolol. The therapy is amid at blocking β1 receptor on the other hand β2 receptor cause well known side effects like Vasocostriction, Bronchoconstriction, Delayed response to Hypoglycemia.

Clinical Studies
β blocker may increase risk of diabete., Dr Frederic Brancati studied data on 12550 non diabetic patients from 45 to 65 years of age, patients were screened for diabetes patients with high blood pressure were 2-1/2 times more likely than others to develop type-2 diabetes . After adjusting for other factors, patients taking a thiazide diuretic, an ACE inhibitor,beta blocker were compared however the risk of diabetes was 1-1/4 times higher for patients using beta blocker. In another study it was report ed that4 Atenolol may reduce INSULIN SENSITIVITY in non diabetic hypertensive patients (Reneland et el 2000 .). A large prospective study was conduct who did not have diabetes and that designed to examine the independent relation between the use of antihypertensive medication and risk of development of diabetes type- 25. Patients with hypertension who were taking thiazide diuretic , ACE Inhibitor, calcium channel blocker were found not to be at a greater risk of type-2 diabetes and who were taking beta blocker had a 28 percent higher risk of type-2 diabetes mellitus then hypertensive patients6

Potential mechanisms by which beta blocker and Diuretics may contribute to the development of diabetes include
1. Signal transduction and impair insulin stimulated uptake of glucose in peripheral tissue
2. Attenuation of the beta receptor mediated release of insulin from pancreatic beta cell
3. Decreased blood flow through the microcirculation in skeletal muscle tissue leading to decreased insulin sensitivity.
4. Weight gain

Signal transduction of insulin receptor
Stimulation of the insulin receptor results in the activation of two major pathways.
1. Mitogen activated protein kinase cascade
2. Phosphatidylinositol-3 kinase ( PI-3 KINASE)

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Blood pressure | SBP mm Hg | DBP mmHg | Follow up recommendations
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Normal | <120 | <80 | After every 2 years
Pre Hypertension | 120-139 | 80-90 | 1 YEAR
Stage 1 Hypertension | 140-159 | 90-99 | 2 MONTHS
Stage 2 Hypertension | >160 | >100 | 1 week

Table no 1: Classification and Management of blood pressure

- Non selective β blocker (β₁ and β₂): Propranolol, Pindolol.
- Selective β₁ blocker: Atenolol, Metoprolol.
- Non Selective and vasodilating (β₁, β₂ and α₁): Labetalol, Carvedilol
- Vasodilating (NOpath way): Nebivolol

Table no 2: Classification of some commonly use β blockers

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Fig. 1 Structure and function of the insulin receptor. Binding of insulin to the α-subunits leads to activation of the intracellular tyrosine kinase (β-subunit) by autophosphorylation. The insulin receptor substrates (IRS) bind via a phospho-tyrosine binding domain to phosphorylated tyrosine residues in the juxtamembrane domain of the β-subunit. The receptor tyrosine kinase then phosphorylates specific tyrosine motifs (YXXM) within the IRS. These tyrosine phosphorylated motifs serve as docking sites for some adaptor proteins with SRC homology 2 (SH2) domains like the regulatory subunit of PI3-kinase.

Fig. 2 Signal transduction of the insulin receptor. Activation of the insulin receptor leads to stimulation of the PI 3-kinase pathway. Generation of P3-phosphorylated PI-phospholipids mediates the effect of insulin on glucose transport, cell survival, protein synthesis, glycogen synthesis and gene expression. The protein kinase Akt plays a central role in the regulation of these PI 3-kinase dependent processes.
It is now evident that treatment with β adrenergic antagonist is associated with an increased risk of NIDDM. β-adrenergic antagonist may impair insulin – stimulated uptake of glucose in peripheral tissues. Propranolol is a non selective β adrenergic antagonist with no ISA. In studies using the hyperinsulinemic-euglycemic clamp technique, glucose uptake in peripheral tissue decreased by 32 percent in propranolol treated patients. Non selective β adrenergic antagonist with ISA pindolol glucose uptake diminished by 17 percent.. Dilevalol a more pronounced β2 - adrenergic agonist did not alter insulin sensitivity. Selective β adrenergic antagonist such as atenolol and metoprolol decrease glucose uptake by about 25 percent. The decrease in sensitivity to insulin is associated with increases in plasma concentration of insulin and glucose after the ingestion of glucose. The increase in plasma insulin concentration compensates for the worsening of insulin resistance, and the increase in the glucose concentration indicates that the compensation is not fully effective. Reduction in glucose uptake by different β blockers is shown in table 3.

<table>
<thead>
<tr>
<th>Name of drug</th>
<th>Activity</th>
<th>Glucose up take in peripheral tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>Non selective β adrenergic antagonist with no ISA</td>
<td>32 % ↓</td>
</tr>
<tr>
<td>Pindolol</td>
<td>Non selective β adrenergic antagonist with ISA</td>
<td>17% ↓</td>
</tr>
<tr>
<td>Dilevalol</td>
<td>B2 adrenergic agonist</td>
<td>No change</td>
</tr>
<tr>
<td>Atenolol</td>
<td>selective β adrenergic antagonist</td>
<td>25% ↓</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>selective β adrenergic antagonist</td>
<td>25% ↓</td>
</tr>
</tbody>
</table>

Table no 3: showing reduction in glucose uptake by various β blockers

**Signal transduction and Genetic bases of type - 2 Diabetes**

Few studies have addressed the genetic bases of type - 2 Diabetes. Many candidate genes for type -2 diabetes have been proposed based on their role in insulin action insulin resistance .The insulin receptor is a trans-membrane receptor tyrosine kinase located in the plasma membrane of insulin sensitive cells like adipocytes, myocytes, hepatocytes. Insulin Receptor is encoded by a single gene and consists of 22 exons (exon 1-11 = α subunit , exon 12-22 = β subunit) tyrosin residues in catalytic domain(y1158,y1162,y1163 of human insulin receptor gene) are essential for the kinase activity. Lirko- mice with a liver-specific insulin receptor knockout show sever insulin resistance and hyperglycemia due to an increased hepatic gluconeogenesis Mirko-Mice with a skeletal muscle – specific insulin receptor knock out have normal blood glucose tolerance but elevated serum fatty acid and tryglycerides.8 This data emphasize the importance of insulin action for glucose homeostasis and indicate that the INSR plays an important role in the central regulation of body weight (32). IRS-1 is a signaling protein that acts as a docking and activation site for multiple signal transducing molecules that control cellular growth and metabolism(x). Four different mammalian IRS iso type have been identified ( IRS1,4 IRS1; Knock out mice mild state of insulin resistance with out Diabetes IRS2; severe insulin resistance with Diabetes and impaired pancreatic function IRS3. Normal IRS4; mild glucose intolerance and growth retardation in male animals. Data suggest that the major effects of insulin on metabolism are mediated via IRS1 and IRS2 ; (33,8) Many candidate genes for type 2 diabetes have been proposed based on their role in insulin action or insulin resistance (1–4). Among these, the gene encoding the insulin receptor substrate-1 (IRS-1) protein located on chromosome 2q35–q36.1 has been studied extensively with inconclusive results (5–24). IRS-1 is a signaling protein that acts as a docking and activation site for multiple signal transducing molecules that control cellular growth and metabolism (9). One of the most common mutations in the IRS1 gene is in codon 972, where a point mutation causes a change from glycine (GGG) to arginine (AGG) (10,11). This mutation is located between tyrosine phosphorylation motifs in the IRS1 -1 gene, but is not within any of the tyrosine phosphorylation or ATP binding sites (12)

**Effects of β adrenergic antagonist treatment on blood flow**

Stimulation of the peripheral uptake of glucose is strongly correlated with increased peripheral blood flow. With blockage of β1 adrenergic receptors cardiac out put decreases and compensatory vasoconstriction occurs. In patients receiving a drug with simultaneous agonist effect on β2 adrenergic receptors in the vessel wall , such as Pindolol or Dilevalol vasodilatation predominant.(13, 14)

**Effects of antihypertensive treatment on weight gain**

The effects on body weight can be in large part explained by changes in energy metabolism Several investigators have shown that total energy expenditure may be reduced 4% to 9% with β-blocker treatment. In a recent study, it was showed that β-blockade reduces the basal metabolic rate by 12% in obese hypertensive patients; compared with obese hypertensive patients receiving other antihypertensive agents (Astrup et al) provided evidence for a β2-adrenergic receptor–mediated facultative thermogenic component in skeletal muscle and a β1-adrenergic receptor–mediated component in nonmuscle tissue. Furthermore, several investigators reported a 25% reduction in the thermogenic response to a mixed or carbohydrate-enriched meal after β-blockade. Consistent with this finding, β-blockade also
Reduced the meal-induced increase in forearm oxygen consumption by 23%. Interestingly, inhibition of sympathetic activity with the centrally acting agent clonidine also resulted in a 33% reduction in the thermogenic response to food (15). Although the thermogenic effect of food accounts for only a relatively small proportion of daily energy expenditure (3% to 10%), small differences in thermogenic effects of food over longer periods of time may significantly contribute to the development and/or maintenance of obesity. (16, 13, 17, 18, 19, 15, 20)

Diuretics
Diuretics promote the urinary excretion and use as antihypertensive drug. Interaction with sodium absorption in the DCT by thiazide diuretics is effective as first line therapy of hypertension. Initial reduction in blood pressure appears to be due to reduced plasma volume, reduced venous return and cardiac output. The prolonged effect of thiazides to reduce blood pressure is related to a total peripheral resistance.

Mechanism:
Thiazide diuretic appear to disturb glycemic control in a dose dependent fashion by reducing insulin secretion and peripheral insulin sensitivity. (21, 22, 23, 24, 25). Development of hypokalemia appers to be important because the use of potassium supplement prevent Thiazide induced glucose intolerance (23, 24, 25). ATP-sensitive potassium KATP channels regulate insulin secretion by coupling the metabolic state of the cell to membrane potential. Elevation of blood glucose level leads to an increase in the ATP to ADP ratio and a decrease in KATP channel permeability that in turn leads to membrane depolarization, activation of voltage-dependent calcium channels, Ca2_ influx into the cell, and finally insulin exocytosis (26) Genetic bases A recent study found an association of the SUR1 and Kir6.2 genes with type 2 diabetes, but the contribution of different single nucleotide polymorphisms (SNPs) to the risk of type 2 diabetes remained unclear (27). A silent AGG1273AGA polymorphism of the SUR1 gene has been associated with elevated insulin levels in nondiabetic subjects (28) and with increased prevalence of type 2 diabetes in French Caucasians (29). Additionally, this polymorphism has been associated with type 2 diabetes and gestational diabetes in Finnish subjects (30). In contrast, SUR1 promoter SNPs have not been associated with increased risk of diabetes or altered -cell function (31). The E23K polymorphism of the Kir6.2 gene has been found to be consistently associated with increased diabetes risk in British and French subjects (32,33,34).

Effects of other antihypertensive treatment
Other classes of antihypertensive like Calcium channel blocker, Angiotensin – converting – enzyme inhibitors drugs do not affect insulin sensitivity both dihydropyridine and long acting non dihydropyridines calcium antagonist have shown .Metabolic benefits with effects on insulin sensitivity and insulin secretion (35, 36 ). Some animal (37, 38, 39) and human (40) studies have shown that long term ACE inhibition or angiotensin receptor blocker increases whole body insulin sensitivity under experimental conditions. More over, some study (41) have shown skeletal muscle glucose uptake is diminished in transgenic hypertensive rats (Ren-2) that over produce tissue angiotensin-2 and that this is prevented with ARB

Conclusion
It concluded that in case of hypertension using β adrenergic antagonist and Diuretic as first line therapy is associated with risk of NIDDM due to weight gain. Attenuation of the beta receptor mediat-ed release of insulin from pancreatic beta cell, Decreased blood flow through the microcirculation in skeletal muscle tissue leading to decreased insulin sensitivity and impair insulin stimulated uptake of glucose in peripheral tissues.

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