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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 Hypertrophy[1]. 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 (7^{th}) 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 (JNC ^{7}) [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 β_1 receptor on the other hand β_2 receptor cause well known side effects like Vasoconstriction, Bronchoconstriction, Delayed response to Hypoglycemia.

Clinical Studies

beta blocker may increase risk of diabetes, .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 reported that[4] Atenolol may reduce INSULIN SENSITITY 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- 2[5]. Patients with hypertension who were taking thiazide diuretic , ACE Inhibitor, calcium channel blocker were found not to be at a grater risk of type -2 diabetes and who were taking beta blocker had a 28 percent higher risk of type-2 diabetes mellitus then hypertensive patients[6]

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 path ways.

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
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 (β_1 and β_2)	Propranolol, Pindolol ,
Selective β_1 blocker	Atenolol, Metoprolol,
Non Selective and vasodilating (β_1, β_2 and α_1)	Labetalol, Carvedilol
Vasodilating (NOpath way)	Nebivolol

Table no 2: **Classification of some commonly use β blockers**

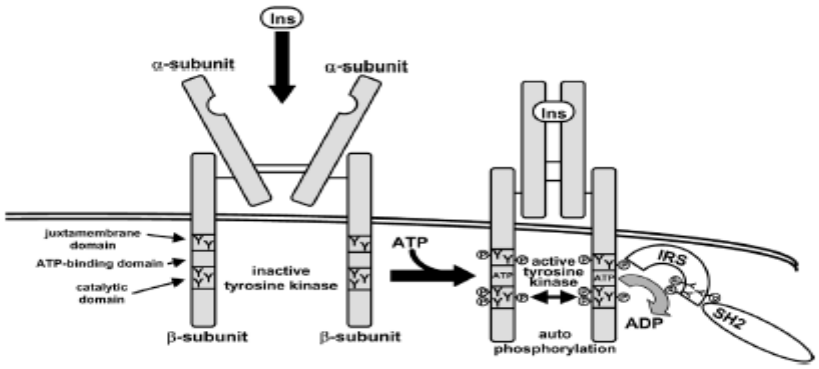

Fig. 1 Structure and function of the insulin receptor. Binding of insulin to the α-subunits leads to activation of the intracellular tyrosine kinase (β-subunit) by autophosphorylation. The insulin receptor substrates (IRS) bind via a phospho-tyrosine binding domain to phosphorylated tyrosine residues in the juxtamembrane domain of the β-subunit. The receptor tyrosine kinase then phosphorylates specific tyrosine motifs (YMxM) 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 PI 3-kinase.

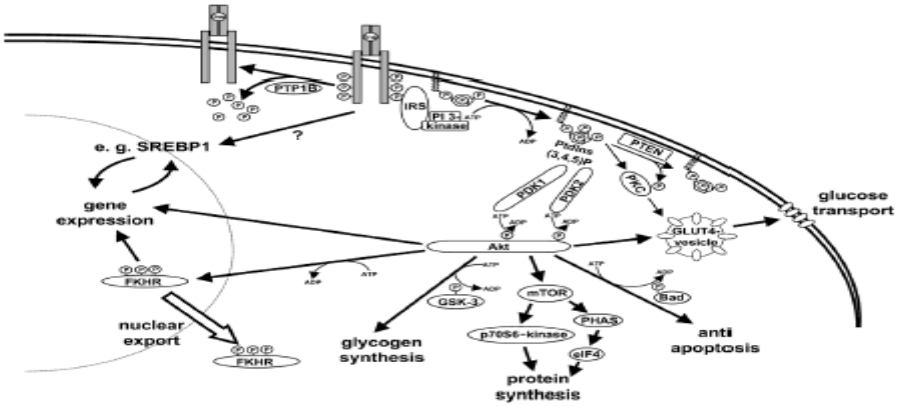

Fig. 2 Signal transduction of the insulin receptor. Activation of the insulin receptor leads to stimulation of the PI 3-kinase pathway. Generation of 3'-phosphorylated PI-phospholipids mediates the effect of insulin on glucose transport, cell survival, protein synthesis, glycogen synthesis and gene expression. 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 up take 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 β_2 -adrenergic agonist did not alter insulin sensitivity. Selective β adrenergic antagonist such as atenolol and metoprolol decrease glucose uptake by about 25 percent [7]

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 up take by different β blockers is shown in table 3

Name of drug	Activity	Glucose up take in peripheral tissue %
Propranolol	Non selective β adrenergic antagonist with no ISA	32 % ↓
Pindolol	Non selective β adrenergic antagonist with ISA	17% ↓
Dilevalol	B_2 adrenergic agonist	No change
Atenolol	selective β adrenergic an-	25% ↓

	tagonist	
Metoprolol	selective β adrenergic antagonist	25% ↓

Table no 3: showing reduction in glucose up take 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 transmembrane receptor tyrosine kinase located in the plasma membrane of insulin sensitive cells like adipocytes, myocytes, hepatocytes. Insulin .Receptor is encoded by a single gene that is located on human chromosome 19 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 knock out show sever insulin resistance and hyperglycemia due to an increased hepatic gluconeogensis Mirko- Mice with a skeletal muscle – specific insulin receptor knock out have normal blood glucose tolerance but elevated serum fatty acid and tryglycerides8. 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 (IRS_1-4)
IRS_1- Knock out mice mild state of insulin resistance with out Diabetes
IRS_2- severe insulin resistance with Diabetes and impaired pancreatic function
IRS_3- Normal
IRS_4- mild glucose intolerance and growth retardation in male animals
Data suggest that the major effects of insulin on metabolism are mediated via IRS_1 and IRS_2 (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 *I R S - 1* 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 *I R S - 1* gene, but is not within any of the tyrosine phosphorylation or ATP binding sites (12)

Effects of ß adrenergic antagonist treatment on blood flow
Stimulation of the peripheral uptake of glucose is strongly correlated with increased peripheral blood flow. With blockage of β_1 adrenergic receptors cardiac out put decreases and compensatory vasoconstriction occurs. In patients receiving a drug with simultaneous agonist effect on β_2 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 ß-blocker treatment. In a recent study, it was showed that ß-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 $ß_2$-adrenergic receptor–mediated facultative thermogenic component in skeletal muscle and a $ß_1$-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 ß-blockade. Consistent with this finding, ß-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 effect 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 execretion and use as antihypertensive drug. Interference with sodium absorption in the DCT by thiaziade 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,). Development of hypokalemia appers to be important because the use of potassium supplement prevent Thiazide induce glucose intolerance (23, 24, 25). ATP-sensitive potassium KATPchannels 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 blockage 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 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.

References

1. Brenner GM, Stevens CW. Antihypertensive Drugs. In Brenner GM, Stevens CW editors. Pharmacology. Elsevier :2nd Ed 2006 p.
2. Shafiq N, Malhotra S,and,. Pandhi P JNC: A Critical Appraisal **Drugs bulletin** october2003 volume27(4)
3. Joint National Committee on Prevention, Detection and Treatment of High Blood Pressure. The seventh report of the Joint National Committee on Prevention, Detection and Treatment of High Blood Pressure (JNCVII). **JAMA** 2003;**289**:2560-2572
4. Dr Frederic Brancati ,**N Engl J Med** 2000; **342:**905-912,969-970 .
5. Gress TW, Nieto FJ, Shahar E et al: Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. **N Engl J Med** 2000; **342(13):**905-912.

6. Kunz I, Schorr U, Klaus S, Sharma AM. Resting metabolic rate and substrate use in obesity hypertension. *Hypertension.* 2000;36:26–32
7. Stefan Offermanns, Walter Rosenthal, "Encyclopedic Reference of Molecular pharmacology", Edition 2004, Publisher- Springer-Verlag Berlin Heidelberg. P.No.-494 & 496
8. Myers MGJ, White MF, The new elements of insulin signaling: insulin receptor substrate-1 and proteins with SH2 domains, ***D i a b e t e s*** 1993 **42:**643–650
9. Imai Y, Fusco A, Suzuki Y, Lesniak MA, D'Alfonso R, Sesti G, Bertoli A, Lauro R, Accili D, Taylor SI, Variant sequences of insulin receptor substrate-1 in patients with non insulin-dependent diabetes mellitus. ***J Clin Endocrinol Metab*** 1994 **79:**1655–1658
10. Almind K, Bjorbaek C, Vestergaard H, Hansen T, Echwald S, Pedersen O: Amino acid polymorphisms of insulin receptor substrate-1 in non- insulindependent diabetes mellitus. ***L a n c e t*** 1993 **342:**828–832
11. Armstrong M, Haldane F, Taylor RW, Humphriss D, Berrish T, Stewart MW, Turnbull DM, Alberti KG, Walker M, Human insulin receptor substrate-1: variant sequences in familial non-insulin-dependent diabetes mellitus. ***D i a b e t Med*** 1996 **13:**133–138,
12. Acheson K, Jequier E, Wahren J. Influence of beta-adrenergic blockade on glucose- induced thermogenesis in man. ***J Clin Invest***. 1983; **72:**981–986.
13. Buemann B, Astrup A, Madsen J, Christensen NJ. A 24-h energy expenditure study on reduced-obese and nonobese women effect of beta-blockade. ***Am J Clin Nutr***. 1992; **56:**662–670.
14. Schwartz RS, Jaeger LF, Veith RC. Effect of clonidine on the thermic effect of feeding in humans. ***Am J Physiol***. 1988; **254:**R90–R94.
15. Van Baak MA, Bohm RO, Arends BG, van Hooff ME, Rahn KH. Long-term antihypertensive therapy with beta-blockers: submaximal exercise capacity and metabolic effects during exercise. ***Int J Sports Med***. 1987**; 8:**342–347
16. De Jonge L, Garrel DR. Role of the autonomic nervous system in the thermogenic response to food in lean individuals**.** ***Am J Physiol***. 1997;**272:**E775–E780
17. Welle S, Campbell RG. Stimulation of thermogenesis by carbohydrate overfeeding. ***J Clin Invest***. 1983; **71:**916–925
18. Astrup A, Simonsen L, Bulow J, Madsen J, Christensen NJ. Epinephrine mediates facultative carbohydrate-induced thermogenesis in human skeletal muscle**.** ***Am J Physiol.*** 1989; **257:**E340–E345.
19. Perez-Stable E, Caralis PV. Thiazide-induced disturbances in carbohydrate, Lipid and potassium metabolism**.** ***Am Heart J.*** 1983;**106(**1, pt 2):245-251
20. Harper R, Ennis CN, Sheridan B, Atkinson AB, Johnston GD, BellPM. Effects of low dose versus conventional dose thiazide diuretic on insulinaction in essential hypertension. ***BMJ.*** 1994; **309:**226-230.
21. Fletcher A, Amery A, Birkenhager W, et al. Risks and benefits in the trial of the European Working Party on High Blood Pressure in the Elderly .**J *Hypertens***. 1991; **9:**225-230.
22. Padwal R, Laupacis A. Antihypertensive therapy and incidence of type 2 diabetes: a systematic review. ***Diabetes Care***. 2004; **27:**247-255
23. Gorden P, Sherman BM, Simopoulos AP. Glucose intolerance with hypokalemia: an increased proportion of circulating proinsulin-like componant ***.J Clin Endocrinol Metab***. 1972; **34:**235-240.
24. Helderman JH, Elahi D, Andersen DK, et al. Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. ***Diabetes***. 1983; **32:**106-111
25. Seino S, Miki T Physiological and pathophysiological roles of ATPsensitive K_ channels**. Prog Biophys Mol Biol** 2003 **81:**133–176
26. Florez JC, Burtt N, de Bakker PIW, Almgren P, Tuomi T, Holmqvist J, Gaudet D, Hudson TJ, Schaffner SF, Daly MJ, Hirschhorn JN, Groop L, Altshuler D Haplotype structure and genotype-phenotype correlations of the sulfonylurea receptor and the islet ATP-sensitive potassium channel gene region. **Diabetes** 2004 **53:**1360–136
27. Goksel DL, Fischbach K, Duggirala R, Mitchell BD, Aguilar-Bryan L, Blangero J, Stern MP, O'Connell P Variant in sulfonylurea receptor-1 gene is associated with high insulin concentrations in non-diabetic Mexican Americans: SUR-1 gene variant and hyperinsulinemia**. Hum Genet** 1998 **103:**280–285

28. Reis AF, Ye WZ, Dubois-Laforgue D, Bellanne-Chantelot C, Timsit J, Velho G Association of a variant in exon 31 of the sulfonylurea receptor 1 (SUR1) gene with type 2 diabetes mellitus in French Caucasians**. Hum Genet** 2000 **107:**138–144
29. Rissanen J, Markkanen A, Ka¨rkka¨inen P, Pihlajama¨ki J, Keka¨la¨inen P, Mykka¨nen L, Kuusisto J, Karhapa¨a¨ P, Niskanen L, Laakso M Sulfonylurea receptor 1 gene variants are associated with gestational diabetes and type 2 diabetes but not with altered secretion of insulin**. Diabetes Care** 2000 **23:**70–73
30. Hansen T, Ambye L, Grarup N, Hansen L, Echwald SM, Ferrer J, Pedersen O Genetic variability of the SUR1 promoter in relation to _-cell function and type II diabetes mellitus**. Diabetologia** 2001 **44:**1330–1334
31. Hani EH, Boutin P, Durand E, Inoue H, Permutt MA, Velho G, Froguel P Missense mutations in the pancreatic islet _ cell inwardly rectifying K_ channel gene (KIR6.2/BIR): a meta-analysis suggests a role in the polygenic basis of type II diabetes mellitus in Caucasians**. Diabetologia** 1998 **41:**1511–1515
32. Gloyn AL, Hashim Y, Ashcroft SJ, Ashfield R, Wiltshire S, Turner RC Association studies of variants in promoter and coding regions of _-cell ATPsensitive K-channel genes SUR1 and Kir6.2 with type 2 diabetes mellitus (UKPDS 53). **Diabet Med** 2001 **18:**206–212
33. Gloyn AL, Weedon MN, Owen KR, Turner MJ, Knight BA, Hitman G, Walker M, Levy JC, Sampson M, Halford S, McCarthy MI, Hattersley AT, FraylingTM Large-scale association studies of variants in genes encoding the pancreatic _-cell KATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. **Diabetes 2003 52:**568–572
34. Koyama Y, Kodama K, Suzuki M, Harano Y. Improvement of insulin Sensitivity by a long-acting nifedipine preparation (nifedipine-CR) in patients with essential hypertension. ***Am J Hypertens*.** 2002; **15:**927-931
35. Yagi S, Goto S, Yamamoto T, Kurihara S, Katayama S. Effect of cilnidipine on insulin sensitivity in patients with essential hypertension. ***Hypertens Res***. 2003; **26:**383-387.
36. *Henriksen TR, Jacob*.S.Kinnick TR.Teachey MK . Krekler M. selective angiotensin II receptor receptor antagonism reduces insulin resistance in obese Zucker rats . **Hypertension.**2001: **38:** 884-890
37. *Navarrow*.Cid. j.Maeso R. Perez-Vizeaino F.et al. Effects of losartan on blood pressure, metabolic alterations and vascular reactivity in the fructose induced hypertensive rat**. Hypertension**.1995:**26(6.pt2):**1074-1078
38. *Sasaki K*. KushiroT .Nakagawa S. Kanmatsuse K. Effects of angiotensinII receptor antagonist on insulin sensitivity and sympathetic activity in spontaneously hypertensive rats [in Japanese]. **Nippon jinzo Gakkai Shi**. 1999; **41:**692-696
39. *Higashiura K*. ura N . Miyazaki Y . Shimamoto K. Effect of an angiotensinII receptor antagonist. Candesartanon insulin resistance and pressor mechanisms in essential hypertension**. J Hum Hypertension**. 1999; **13(suppl 1):**571-57
40. *Kinnick TR*. Youngblood EB .O Keefe MP. Saengsirisuwan V. Teachey MK. Henriksen EJ . Modulation of insulin resistance and hypertension by voluntary exercise training in the TG(Mren2) 27 rat**. J Appl Physiology** 2002 ;**93:**805-812