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Beneficial effects of RAS blockers in prediabetics with a hypertension-An observational cohort study

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ABSTRACT

Hypertensive patients have a high prevalence of prediabetes and type II Diabetes mellitus. As per International Diabetic Federation, it has been estimated that more than 470 million people will have prediabetes by 2030. Approximately 5-10% of prediabetes progresses to overt diabetes mellitus, with the same proportion converting back to normoglycemia. In patients who are on Renin-Angiotensin System [RAS] blockers either an Angiotensin converting enzyme inhibitor (ACEI) or an Angiotensin receptor blocker (ARB) would slow down the progress of prediabetic state to overt or frank diabetes mellitus. This was a prospective, observational cohort study and a total of 125 hypertensive patients with impaired glucose tolerance were included in the study who were either on ACE inhibitor or ARB monotherapy. An oral Glucose Tolerance Test (GTT) was done at baseline for screening prediabetic patients, then a periodical assessment of glycemic indices, (fasting blood sugar, 2 hr postprandial blood sugar, and glycosylated hemoglobin), lipid profile, and complication status during the study period were evaluated every 3 months for18months. At the end of 1½ years, for patients belonging to the age group 18-54 years the FBS, PPBS, and HbA_{1C} levels decreased significantly when the RAS blocking drugs (ACEIs and ARBs) were used continuously for 1 year and then they got stabilized. The beneficial effect was seen more in the younger age group 18-54 years old patients. Male above 54 years and females above 49 were resistant to the beneficial effects. In hypertensive patients with impaired glucose tolerance, the blockade of RAS with either ACE inhibitor or ARB has a significant preventive effect on the progression of Type II DM. It may be concluded from the finding of the present study that younger hypertensive patients (18-54 years) of either sex if found to be pre-diabetic may be administered ACEI or ARB as suitable for them. The treatment should be continued vigorously for one year and then it may be maintained to continue the beneficial effect.

1. Introduction

Prediabetes is an intermediate state in which glycaemic indices remain above normal but below the diabetic threshold and includes IFG (impaired fasting glucose) and IGT (impaired glucose tolerance). It has an increased risk of developing overt diabetes mellitus which is the major metabolic disease of modern times and responsible for the majority of morbidity and mortality worldwide (Ruilope and Segura, 2003). The major adverse outcomes of diabetes mellitus are the outcome of macro and microvascular complications (Grundy et al., 1999). Diabetes mellitus is a metabolic cum vascular disorder with the common elements of hyperglycemia and impaired glucose tolerance due to disturbances in carbohydrate, lipid, and protein metabolism (Kumar and Clark, 2002; Beverley and Eschwège, 2003) resulting from defects in insulin secretion, impaired effectiveness of insulin action, or both. Though hypertension is the leading cause of morbidity and mortality worldwide, there is a concomitant increased risk of developing type II diabetes mellitus (Arauz-Pacheco et al., 2003; Conroy et al., 2003). Hypertensive patients are 2.5 times more likely to develop diabetes than those who are normotensive (Gress et al., 2000). Hypertension and frank diabetes are more likely to

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develop complications, hence appropriate blood pressure control in these individuals reduces the risk. With timely and effective intervention by screening prediabetic state and using RAS blockers the progression to overt diabetes can be interrupted. Studies have revealed that the progression rate was 11.8 and 17.0 per100 person-year particularly in the first year (Gress et al., 2000; Nichols et al., 2007).

Hypertension, obesity, and insulin resistance cluster together in the pathogenesis of metabolic syndrome too (Ruilope and Segura, 2003; Grundy et al., 1999; Gress et al., 2000). There is no significant difference in prevalence in men and women, and around half of all individuals with IGT are aged under 50 years. A proportion of 5-10% of people per year with pre-diabetes will progress to diabetes, with the same proportion converting back to normoglycemia. Hypertensive diabetic patients are at increased risk of diabetes-specific complications including retinopathy and nephropathy (Padwal and Laupacis, 2004). So disease excursion starts from normal glucose tolerance through impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) to frank diabetes mellitus, which may be non-insulin requiring, insulin-requiring for control, and insulin-requiring for survival. Evidence-based studies suggest that those who have IGT /IFG and one or more components of risk factors like hypertension, obesity, and BMI>25 kg/m^2 are more likely to progress to overt diabetes (Unwin et al., 2002).

Hyperinsulinemia and insulin resistance have a common pathophysiological disturbance that plays a causal role in both essential hypertension and Types 2 diabetes (Julius et al., 2004). RAS itself plays a crucial role in the development of diabetes. Hyperactivity appears to be linked to decreased insulin and glucose delivery to the peripheral skeletal muscle and impaired transport of glucose and response to insulin signaling pathways, thus increasing insulin resistance (Jandeleit-Dahm et al., 2005). Local pancreatic RAS activation within the islets may represent an independent mechanism for the progression of islet cell damage in diabetes. Hence, impaired pancreatic islet function may predominate quantitatively over peripheral insulin resistance in IGT (Ferrannini et al., 2003). Hence, ACEIs and ARBs are likely to be of benefit in the prevention of progression of prediabetes to overt diabetes (Jandeleit-Dahm et al., 2005; Ibrahim, 2006). Many studies have suggested that there is a close relationship between RAS and the pathogenesis of IR. Hence many guidelines worldwide recommend ACEI /ARBs as first-line antihypertensive medication for diabetic hypertensive patients (Dahlöf et al., 2005; Hansson et al., 1999).

There is also growing evidence that enhanced activation of the Renin-Angiotensin-Aldosterone System (RAAS) is a key factor in the development of endothelial dysfunction and hypertension. IR is induced by activation of the RAAS and results in increased production of reactive oxygen species (ROS). This occurs in cardiovascular tissue and in other target tissues of insulin. Prediabetic state or IR along with HTN contributes to the development of oxidative stress, endothelial dysfunction, atherosclerosis, CVD, CKD, and other complications. Pharmacological intervention with RAS blockers not only improves blood pressure but also has a beneficial effect on inflammation, oxidative stress and insulin sensitivity, glucose homeostasis, and delays the progress of new pre-diabetes to frank diabetes.

2. Material and methods

This study was undertaken to evaluate the effects of ACEIs and ARBs on various parameters of hypertensive patients with Impaired Glucose Tolerance or impaired fasting glucose patients by periodically assessing their glycemic status during the study period. The study was conducted in IMS and SUM Hospital, Bhubaneswar. It was an observational cohort study. All the hypertensive patients having systolic blood pressure>130mm of Hg and diastolic blood pressure >85mm of Hg, both old and recent onset, attend the Cardiology/Medicine outpatient department (OPD).

Out of the target population, a total of 125 patients were selected on the basis of exclusion, inclusion criteria, and parameter study (personal history, physical examination, biochemical parameters). Inclusion criteria include the following:

1. Adult patients between 18-70 yrs of age.
2. Both male and female.
3. Systolic blood pressure≥130 mm of Hg and Diastolic blood pressure≥85 mm of Hg.
4. Pre-diabetic (PreDM) patients with FBS between 100mg/dl (5.6mmol/l) to 125mg/dl (6.9mmol/l), Oral glucose tolerance test (OGTT)/ postprandial blood glucose between 140mg/dl (7.8 mmol/l) and 199mg/dl (11.0mmol/l) two hrs after a 75mg oral glucose challenge.
5. Individuals with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) and HbA1C between 5.7% to 6.4%

Exclusion criteria include the following:

1. Established cases of Type1 Diabetes mellitus, Type 2 Diabetes mellitus
2. Patients with a history of Type 4 diabetes mellitus (gestational diabetes mellitus GDM) and pregnancy-induced hypertension (PIH).
3. Patients taking antihypertensive drugs other than Angiotensin-Converting Enzyme Inhibitor and/or Angiotensin Receptor Blocker.
4. Other specific types of Diabetes or Type3 Diabetes mellitus
5. Established cases of Chronic Kidney Disease, Liver disease, and Pancreatitis.
6. Patients with associated endocrine disorders such as chronic pancreatic diseases, overproduction of pituitary, adrenal hormones, hyperthyroidism, hypercortisolism, acromegaly,

pheochromocytoma, and polycystic ovarian disease.
7. Patients taking drugs interfering with blood glucose level, drugs causing hyperglycemia like levodopa, steroids, thiazides, phenytoin, somatostatin, diltiazem, β-blockers, morphine, didanosine, or drugs causing hypoglycemia like sulfonylureas, glitinides, pramlintide, quinine, quinidine, insulin, clarithromycin, bromocriptine.
8. Patients refused to sign in the consent form.
9. Patients who come for follow-up < 1 year (visit less than four times, at an interval of 3 months).
10. Patients who developed complications during the study period were not followed up further.

Statistical Analysis: In this observational study, parameters like glycemic indices, anthropometric measures, and blood pressure of subjects have been analyzed with the help of SPSS-13 software. Descriptive statistics like frequency distribution, mean, percentiles, and standard deviation were computed for different parameters. For categorical variables, the cross-tab procedure was applied to generate cross-tabulation and chi-square test of association.

Two-way analysis of variance and ANCOVA procedure was followed to study the contribution of factors like age, sex, and joint effect of age and sex, waist circumference, and BMI on dependent variables like FBS, PPBS, HbA_{1C}, TC, TG, LDL, HDL. In all cases, the p-value was taken at 0.05.

3. Results

The age was stratified into three groups,18-34 yrs, 35-54 yrs, and 55-74 yrs. Out of 125 subjects males were 72 (57.6%) and females were 53(43.4%). Out of 72 males, 8.33% were in the age group 18 to 34 yrs, 43.06% were in the age group 35 to 54 yrs and the maximum was in the older age group, i.e., 55 to 74 yrs. The mean age of males was 52.46±12.92 with a minimum age of 22 and a maximum of 70 yrs. Out of 53 female subjects, 7.55% were in the age group 18 to 34 yrs and the maximum was in the age group 35-54 years, i.e., 66.04%. The mean age for females was 48.36±10.42 with a minimum age of 25 and maximum age was 68. When considering for total of 125 subjects 8% of subjects were in the 18 to 34 yrs group and the maximum was from 35 to 54 yrs group was 52.8%. The mean age was 50.72±12.05 (Table 1).

Table 1: Age and sex distribution of study subjects

Age Group (Yrs)	Sex				Total		χ^2, t, df and p-Value
	Male		Female				
	Number	%	Number	%	Number	%	
18 – 34	6	8.33	4	7.55	10	8.00	$\chi^2 = 6.914$ df = 2 p = 0.032
35 – 54	31	43.06	35	66.04	66	52.80	
55 – 74	35	48.61	14	26.42	49	39.20	
Total	72	100	53	100	125	100	
Mean ± S.E.	52.46 ± 1.52		48.36 ± 1.43		50.72 ± 1.08		t = 1.899 df = 123 p = 0.052
Minimum	22		25				
Maximum	70		68				
Range	48		43				

Two types of RAS blocking drugs Angiotensin Receptor Blocker (ARB) or Angiotensin converting enzyme inhibitor (ACEI) were used by the patient continuously throughout the survey. Out of 125 subjects, 59.2% used ARBs, and 40.8% used ACEIs.

All the 125 patients were followed up at an interval of 3 months for 18 months. But the dropout rates were 24.0%, 42.4%, and 61.6% respectively in the 5th, 6th, and 7th visits. Table 2 depicted descriptive statistics of FBS at different points of visits and Fig. 1 illustrated the trend of FBS graphically. There was a steady decline in the mean level of fasting blood glucose from 110.18 mg/dl in the first visit to 101.35 mg/dl in the 7th visit. The 25th, 50th, and 75th percentiles at 1st visit were 104 mg/dl,110.00 mg/dl, and 116.00 mg/dl respectively in the first visit, which has steadily declined to 93mg/dl, 98mg/dl 102.5 mg/dl in the 7th visit.

Table 2: Descriptive statistics of FBS at different points of visits

Visits	1st	2nd	3rd	4th	5th	6th	7th
N	125	125	125	125	95	72	48
Missing	0	0	0	0	30 (24.0%)	53 (42.4%)	77 (61.6%)
Mean	110.18	107.12	105.54	103.39	103.92	101.88	101.35
S. E(Mean)	0.67	0.82	0.79	0.90	1.13	1.20	1.84
S. D.	7.44	9.16	8.86	10.06	10.98	10.21	12.77
Minimum	90	92	90	89	88	84	86
Maximum	126	182	160	156	150	142	140
25th Percentile	104	100	100	99	99	98	93
50th Percentile	110	107	103	100	100	100	98
75th Percentile	116	110	110	108	105	103	102.5

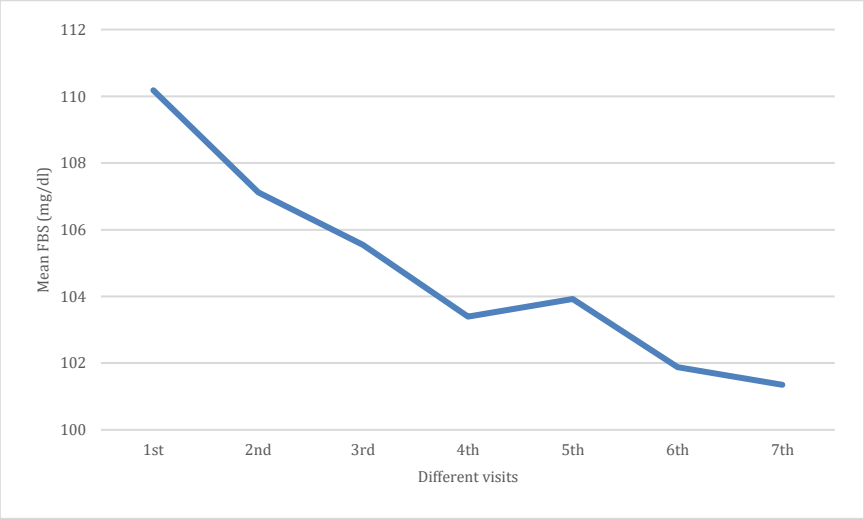

Fig. 1: Mean FBS at different points of visits

The classification of subjects was made into 3 groups based on the blood glucose level. Normal (FBS<100 mg/dl), Pre-diabetic (FBS 100-125 mg/dl) and Diabetic (FBS≥126 mg/dl). There was an increasing trend in the proportion of blood sugar below 100mg/dl from 5.6% to 52.1% between the 1st and 7th visit. This indicated that ACEIs or ARBs had some effect on the control of new-onset diabetes. The proportion of IGT progressing to frank diabetes had increased. In the 1st visit none were the frank case of diabetes, however, in the 7th visit 3 out of 48 were found to be frank diabetic (Table 3).

Table 3: Classification of subjects according to FBS (mg/dl) level at different visits

Visits		1st	2nd	3rd	4th	5th	6th	7th
Normal (<100)	No.	7	2	15	34	29	30	25
	%	5.60	1.60	12.00	27.20	30.53	41.67	52.08
Pre-diabetic (100 - 125)	No.	118	122	108	90	62	40	20
	%	94.40	97.60	86.40	72.00	65.26	55.56	41.67
Diabetic (≥ 126)	No.		1	2	1	4	2	3
	%		0.80	1.60	0.80	4.21	2.78	6.25
Total	No.	125	125	125	125	95	72	48
	%	100	100	100	100	100	100	100

There was a steady decline in mean levels of PPBS from 170 mg/dl in the 1st visit to 146.73 mg/dl in the 7th visit (Table 4). The 25th, 50th, 75th percentile at 1st visit were 160.00mg/dl, 170mg/dl, and 179.50 mg/dl respectively in the 1st visit which had steadily declined to 139.00mg/dl, 140.00mg/dl and 148.00mg/dl. This indicated a steady regression of PPBS levels among the pre-diabetes patients. The stratification was made in 3 groups Normal<140mg/dl, Prediabetic-140-199mg/dl and diabetics>200 mg/dl.

Table 4: (a) Descriptive statistics of PPBS (mg/dl) at different visits; (b) Descriptive statistics of PPBS (mg/dl) by different levels at different visits

Visit	1st	2nd	3rd	4th	5th	6th	7th
N	125	124	125	125	95	71	48
Missing	0	1	0	0	30	54	77
Mean	169.24	164.27	157.48	151.80	151.46	147.77	146.73
Std. Error of Mean	1.13	0.99	1.06	1.26	2.09	1.86	2.44
Median	170	162	155	148	145	143	140
Std. Deviation	12.67	11.03	11.89	14.12	20.38	15.64	16.94
Minimum	141	140	139	136	133	120	129
Maximum	200	189	190	199	280	215	203
25 Percentile	160	157.25	149	142	141	140	139
50 Percentile	170	162	155	148	145	143	140
75 Percentile	179.5	170	163.5	157	151	149	148

(a)

Visit		1st	2nd	3rd	4th	5th	6th	7th
Normal (<140)	No.			1	8	10	9	14
	%			0.80	6.40	10.53	12.68	29.17
Pre-diabetic (140-199)	No.	124	124	124	117	82	61	32
	%	99.20	100	99.20	93.60	86.32	85.92	66.67
Diabetic (>200)	No.	1				3	1	2
	%	0.80				3.16	1.41	4.17
Total	No.	125	124	125	125	95	71	48
	%	100	100	100	100	100	100	100

(b)

The glycosylated Hb level of the study cohort of 125 patients showed a steady decline in the mean of 6.09% to 5.73% on the 7th visit i.e. in the span of 18 months of observation (Table 5). The study cohort was subdivided into normal group HbA_{1C} less than 5.7% which comprised only one subject (0.81%), pre-diabetic (HbA_{1C} 5.7%-6.4%) which comprised 111 subjects (90.24%), and diabetic (HbA_{1C}>6.5%) which comprised 11 subjects (8.94%). In the first visit only one patient out of 123 (0.8%) was having HbA_{1C} of less than 5.7% but in the 7th visit 37 out of 48 constituting 77.1% reported an HbA_{1C} of 6.4% but the proportion of this level remained more or less the same.

Table 5: Distribution of HbA_{1C} (%) by different levels

HbA_{1C} (%)		1st	2nd	3rd	4th	5th	6th	7th
Normal (<5.7%)	No.	1	5	26	67	55	48	37
	%	0.81	4.03	20.80	53.60	57.89	66.67	77.08
Pre-Diabetic (5.7 – 6.4%)	No.	111	108	90	51	30	19	6
	%	90.24	87.10	72.00	40.80	31.58	26.39	12.50
Diabetic (>6.5%)	No.	11	11	9	7	10	5	5
	%	8.94	8.87	7.20	5.60	10.53	6.94	10.42
Total	No.	123	124	125	125	95	72	48
	%	100	100	100	100	100	100	100

There was a decrease in HbA_{1C} levels in all age groups and the glycemic status of patients at different visits showed gradual improvement. On the other hand, there was an increase in the percentage of patients with normal blood sugar levels from 5.6% to 52.08 % and also a decrease in the proportion of pre-diabetic patients from 94.4% on the first visit to 41.67% on the 7th visit. The same was also noticed in the postprandial blood sugar level and HbA_{1C}. However, the proportion of diabetic patients from 0% increased to 6.25% (Table 6).

Table 6: Glycemic status of patients at different visits

Glycemic status		FBS			PPBS			HbA_{1C}		
		1st	4th	7th	1st	4th	7th	1st	4th	7th
Normal	No.	7	34	25	0	8	14	1	67	37
	%	5.60	27.20	52.08	0.00	6.40	29.17	0.81	53.60	77.08
Pre-Diabetic	No.	118	90	20	124	117	32	111	51	6
	%	94.40	72.00	41.67	99.20	93.60	66.67	90.24	40.80	12.50
Diabetic	No.	0	1	3	1	0	2	11	7	5
	%	0.00	0.80	6.25	0.80	0.00	4.17	8.94	5.60	10.42
Total	No.	125	125	48	125	125	48	123	125	48
	%	100	100	100	100	100	100	100	100	100

FBS: Normal <100 mg/dl, Pre-Diabetic 100-125 mg/dl, Diabetic ≥126 mg/dl; PPBS: Normal <140 mg/dl, Pre-Diabetic 140-199 mg/dl, Diabetic ≥200 mg/dl; HbA_{1C}: Normal <5.7 %, Pre-Diabetic 5.7-6.4 %, Diabetic ≥6.5 %

4. Discussion

The present study was undertaken to study the effect of ACE Inhibitors/ARBs on blood glucose levels in hypertensive prediabetic patients by periodic Oral Glucose Tolerance Test (GTT) /FBS, 2hr PPBS, HbA_{1C} and to evaluate the exclusive role of RAS blockade, if any, in relation to other contributing factors such as Age, Sex, BMI, Blood pressure which may have a confounding effect on the outcome. In the clinical research work, several large-scale randomized controlled trials have shown that blockade of RAS with either ACE inhibitors or ARBs significantly reduces the incidence of new-onset diabetes. For this study, the target population was hypertensive adult patients having impaired blood glucose levels (IFG and/or IGT) (45,259). Most of these analyses were, however, post-hoc and endpoints are not predefined or the development of diabetes is not the primary endpoint. Trials with a pre-defined new-onset diabetes endpoint were ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) (Unwin et al. 2002), VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) (Julius et al., 2004).

Patients taking other drugs or suffering from concomitant diseases related to hypertension or developed complications or failed to turn up for observation were excluded from the study. So an observational cohort of 125 patients was selected from the 650 patients who were regularly monitored at 3 months intervals for 12 months (4 monitoring) and 48 patients out of the 125 were monitored for up to 18 months (7 monitoring).

The cohort of 125 patients included 53 (42.40%) females and 72 (57.60%) males who were monitored 4 times in one year. In the female subjects, the most prevalent age group was 35 to 54 years while in males the most prevalent age group was 55 to 74 years. Besides the mean age of females was lower than that of males with p=0.052 which is almost tending to be significant. Thus the prevalence of pre-diabetes among males between 55 to 74 years was more whereas the age of onset for pre-diabetes was early for females (35 to 54 year age group in this study cohort). The prevalence of pre-diabetes increased significantly (p<0.05) with increasing age especially in males as revealed through χ^2 test of association. This was also found in studies done on the prevalence of diabetes and pre-diabetes among men and women in China (Yang et al., 2010), Same result was found in the REGICOR study in the Province of Spain (Masiá et al., 2004; Bhalla et al., 2013). However, in this study percentage of women

was found to be more in the middle age group which could be related to increased BMI.

For glycemic status, 3 parameters were taken that was fasting blood sugar, postprandial blood sugar (2 hrs.)/oral glucose tolerance test (OGTT), and HbA_{1C}. There was a significant increase in the number of euglycemic subjects from 5.6% on the 1st visit to 27.2% on the 4th visit and further increased to 52.8% on the 7th visit. This showed a positive response of ACEIs/ARBs in preventing the progress of prediabetes to overt diabetes.

Similarly, the number of prediabetics had significantly dropped ($p<0.05$) from 94.4% in 1st visit to 72% in the 4th visit and further dropped to 41.67% in the 7th visit within a span of 1½ years. But the number of diabetic patients which was 0% on the 1st visit had progressed to 0.8% on the 4th visit and 6.25% on the 7th visit which was statistically not significant ($p<0.05$). This indicated that the continuation of the treatment of hypertension by RAS blocking drugs improved the glycemic parameter which was reflected in the increase in the percentage of euglycemic subjects and steady regression of the FBS level among pre-diabetic patients. This corresponds to the results of the VALUE trial group by Julius et al. (2004) and Califf et al. (2008) in NAVIGATOR trial that addressed the potential of ARB, and valsartan to protect individuals with IGT or IFG and CVD. After a treatment of 5 years, valsartan decreased the onset of type 2 diabetes by 14%. In the current study use of ACEIs/ARBs continuously for 1 year also showed a delay in the progression of prediabetes to frank diabetes.

The difference between two consecutive visits over time, mean the difference between 1st and 2nd and 3rd till 6th and 7th visit were analyzed following paired t-test. The difference was continuously and steadily increased till the 7th visit. Between the 1st and 7th visit mean difference was 10.22 mg/dl. All these mean differences between 1st and 2nd, 1st and 3rd, 1st and 4th, 1st and 5th, 1st and 6th, 1st and 7th were found statistically significant with p tending to zero. This implied that there was a stabilization of FBS level after 1 year but conclusive inference can only be drawn by following the subjects for a period of time.

Analysis of two-way variance was attempted to assess the effect of independent variables like sex and age on dependent variable FBS at the 4th visit controlling for their FBS level at the 1st visit. Test of between subjects effects revealed that the effect of sex on the sum of the square was insignificant ($p=0.199$) whereas the effect of age group was significant ($p=0.026$). Parameter estimates of the model coefficient for sex were 2.35 in males which indicated that the male subjects had 2.35 higher FBS levels than females but this is not statistically significant and may be due to chance. The estimated coefficient for the age group 18 to 34 yrs and 35 to 54 yrs were 8.42 and 3.73 respectively. This indicated that FBS at the 4th visit was lower by 8.42 and 5.07 on an average for age groups 18 to 34 yrs and 35 to 54 yrs respectively than that of age group 55 to 74 yrs. The significant probability was 0.016 and 0.051 respectively. Pair-wise comparison of FBS at the 4th visit by age group through post hoc test was done which revealed a difference in FBS at 4th visit, significant between 18 to 34 and 55 to 74 yrs. This implied that age groups 18-34 and 35-54 years had a better response than the older age groups. This could be probably due to diminished activity of RAAS with aging.

Similarly, 2 hr. PPBS estimation was done at 3 months intervals in the study cohort. It was found that the number of pre-diabetic patients reduced significantly ($p<0.05$). However, from the 4th to 7th visit there was a significant increase ($p<0.05$) from 94.20% to 66.67%. The number of diabetes patients increased from 0.80% on 1st visit to 4.17% on the 7th visit within a span of 1½ years which was statistically not significant ($p>0.05$). A t-test was done to compare PPBS between different pairs of visits. The mean difference of PPBS between the 1st and 2nd visit to the 1st and 7th visit had steadily increased from 4.97mg/dl to 26.77mg/dl. All these mean differences were statistically significant ($p<0.001$).

This implied that there was an increase in trend in the proportion of PPBS<140mg/dl from 0.80% to 29.20% which supported the hypothesis that the RAS blockers were having pleiotropic effects by decreasing the progression of the disease and this finding was supported (Scheen, 2006) DREAM trial (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication), (Califf et al., 2008) NAVIGATOR Trial, specifically addressed the effect of ACEIs or ARBs on IGT/IFG. In the later trial, there was a significant decrease in PPBS ($p<0.05$) and the incidence of type 2 DM by 14%. Table 7 shows **the** distribution of HbA_{1C} at the 1st, 4th, and 7th visits.

Table 7: Distribution of HbA_{1C} at 1st, 4th and 7th visit

HbA_{1C}	1st	4th	7th
Normal	0.81	53.6	77.08
Pre-diabetic	90.24	40.8	12.5
Diabetic	8.94	5.6	10.42

The glycosylated Hb which was considered a better indicator of overall improvement in the glycemic status of a diabetes patient (268) indicated that there was a significant decrease ($p<0.05$) in the number of pre-DM from 90.24% in 1st visit to 40.80% in 4th visit and 12.50% in 7th visit. The number of normal subjects increased significantly from 0.81% on the 1st visit to 53.60% on the 4th visit and 77.08% on the 7th visit.

Table 8 and Table 9 show ANOVA tests of between-subjects effects and ANOVA: Parameter estimates respectively.

Table 8: ANOVA tests of between subjects effects

Dependent Variable: PPBS (mg/dl) 4th Visit					
Source	Sum of Squares	df	Mean Square	f	p
Corrected Model	1626.56#	7	232.37	1.18	0.322
Intercept	2585.39	1	2585.39	13.09	0.000
1st Visit	220.16	1	220.16	1.11	0.293
Waist Circumference	31.24	1	31.24	0.16	0.692
Sex	0.59	1	0.59	0.00	0.956
Age	858.53	2	429.26	2.17	0.118
Sex * Age	504.53	2	252.27	1.28	0.283
Error	23109.44	117	197.52		
Total	2905141	125			
Corrected Total	24736	124			
#	R^2 = .066 (Adjusted R Squared = .010)				

Table 9: ANOVA: Parameter estimates

Parameter	B	Std. Error	t	Sig.	95% C. I.	
					Lower	Upper
Intercept	126.34	33.06	3.82	0.000	60.85	191.82
1st visit	0.11	0.10	1.06	0.293	-0.10	0.32
Waist Circumference	0.13	0.32	0.40	0.692	-0.50	0.76
Sex						
Male	-4.85	4.52	-1.07	0.286	-13.79	4.10
Female	0#	.	.	.	.	.
Age Sex Interaction						
18 – 34	-13.16	8.00	-1.64	0.103	-29.01	2.69
35 – 54	-8.14	4.48	-1.82	0.072	-17.00	0.73
55 – 74	0#	.	.	.	.	.
Sex Age Interaction						
Male * Age [18 – 34]	5.96	10.26	0.58	0.562	-14.36	26.28
Male * Age [35 – 54]	9.18	5.74	1.60	0.113	-2.19	20.55
Male * Age [55 – 74]	0#	.	.	.	.	.
Female *Age [18 – 34]	0#	.	.	.	.	.
Female * Age [35 – 54]	0#	.	.	.	.	.
Female * Age [55 – 74]	0#	.	.	.	.	.
#	This parameter is set to zero because it is redundant					

ANCOVA procedure was conducted to see the effect of sex, age, waist circumference, and combined effect of sex and age on levels of HbA_{1C} at the 4th visit. It was found that contribution to variation was not significant by waist circumference, sex, and joint effect of sex and age (Table 8). But the age group exhibited a significant contribution. ANCOVA parameter estimates also exhibited significance of coefficient for age group 18 to 34 yrs only. That implied that in the age group 18 to 34 yrs the average level was lower than the other age groups and it was significant statistically ($p<0.05$). (Table 9).

Pairwise comparison of HbA_{1C} levels between different age groups inferred that the mean difference was statistically significant between the 18 to 34 and 55 to 74 yrs of age groups (Table 10). The sum and substance from Table 10, it is revealed that the administration of ACEIs and ARBs decreased the level of HbA_{1C} among the study subjects. From the above analysis, it was found that in all the age groups there was a decrease but regression was faster in the age group 18-34 followed by 35-54 years. The decrease in glycemic parameters for the age group 55-74 was slower. This was established in a Univariate analysis of variance. Hence, the study of the glycemic indices of the hypertensive pre-DM patients treated with RAS Blockers and followed up to 18 months at an interval of 3 months indicated that the FBS, PPBS, and HbA_{1C} of pre-diabetic patients decreased continuously for up to 1 year then the fall was stabilized.

Table 11 shows a comparison of decline in (1st-4th visit) glycemic level by age group in males and females.

Table 10: Pair-wise comparison of HBA_{1C} (%) in the 4th visit at different age groups

Dependent Variable: HbA_{1C} (%) 4th Visit						
(I) Age Group	(J) Age Group	Mean Difference (I-J)	S.E	p #	95% C. I. for Difference(a)	
					Lower	Upper
18 – 34	35 – 54	-0.18	0.10	0.211	-0.42	0.06
	55 – 74	-0.26	0.10	0.038	-0.50	-0.01
35 – 54	18 – 34	0.18	0.10	0.211	-0.06	0.42
	55 – 74	-0.08	0.06	0.534	-0.22	0.06
55 – 74	18 – 34	0.26	0.10	0.038	0.01	0.50
	35 – 54	0.08	0.06	0.534	-0.06	0.22
#	Multiple comparisons: Bonferroni.					

Table 11: Comparison of decline in (1st-4th visit) glycemic level by age group in male and female

Sex	Visits	Age Group (Yrs.)	N	Mean	S.D	S.E.	t	df	p
Male	FBS	< 49	27	5.33	11.89	2.29	0.09	70	0.930
		≥ 50	45	5.07	12.78	1.90			
	PPBS	< 49	27	16.85	21.34	4.11	-0.32	70	0.752
		≥ 50	45	18.29	16.77	2.50			
	HbA_{1C}	< 49	26	0.26	0.33	0.06	-0.70	69	0.485
		≥ 50	45	0.31	0.32	0.05			
Female	FBS	< 49	27	10.37	7.60	1.46	0.87	51	0.386
		≥ 50	26	7.54	14.96	2.93			
	PPBS	< 49	27	21.52	11.68	2.25	2.00	51	0.051
		≥ 50	26	12.35	20.64	4.05			
	HbA_{1C}	< 49	27	0.45	0.25	0.05	1.75	50	0.086
		≥ 50	25	0.31	0.34	0.07			

In order to verify whether the decline in glycemic level was having an association with the pre- and post-menopausal age group of females independent sample t-test was conducted (Table 11). The decline in the FBS, PPBS, and HbA_{1C} between 1st and 4th visit was taken as test variables, and age group<49 yrs and>49 yrs was taken as the factor. The independent t-test was conducted both for males and females. In the male group, it was found that the decline in FBS, PPBS, and HbA_{1C} was almost equal irrespective of age group. Whereas in females the drop in glycemic level was found to be more in 49 yrs (post-menopausal group). Though this decline was not statistically significant lower levels of p values for PPBS (p=0.051) and HbA_{1C} (p=0.086) indicated that in the postmenopausal period female might have had greater resistance to decline in glycemic status.

The close relationship between RAS and IR is not a recent observation. Increased expression of the RAS components and high expression of local RAS elements damage the insulin signaling cascade and contribute to both IR and type 2 diabetes mellitus onset (Dahlöf et al., 2005). RAS also has multiple effects on the central nervous system, skeletal muscle, liver, and adipose tissue that may interfere with insulin action. Studies have shown that ACE inhibitors and ARBs can potentially improve insulin resistance in hypertensive patients compared with other antihypertensive drugs (Hansson et al., 1999).

Hypertension and Type-2 DM are two aspects of underlying metabolic disorders seen especially in South Asian countries including India and the beneficial effect is age-related. RAS blocking drugs may produce certain beneficial effects by their influence on the Renin-angiotensin-aldosterone axis and breaking the insulin resistance. Hence this study may be more therapeutic and beneficial for hypertensive patients with insulin resistance in the younger age group and assist clinicians and health professionals make clinical decisions.

In this study, the limitation was that the cohort group need to be monitored for a considerable period of time to further validate the current findings.

5. Conclusion

This study was an observational cohort study without any control comprising 125 prediabetic hypertensive subjects belonging to both sexes. They were followed at an interval of 3 months up to 1½ years. The anthropometric parameters (age, body mass index, waist circumference), and glycemic indices were evaluated. It was observed that in patients belonging to the age group 18-54 years the glycaemic indices (FBS, PPBS, and HbA_{1C} level) decreased significantly when the RAS blocking drugs (ACEIs and ARBs) were used continuously for 1 year and then they got stabilized. The beneficial effect was seen more in the younger age group 18-54 years old patients. Male above 54 years and females above 49 were resistant to the beneficial effects.

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Compliance with ethical standards

Ethical considerations

Our study design was approved by the Institutional Ethical Committee Hospital, Letter no-IMS SH/IEC/2013/44.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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