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Original Research Article

Epidemiology of prediabetes and prehypertension-progression, regression and interaction

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ABSTRACT

Background: The major portion of the non-communicable diseases is formed by cardiovascular diseases. The two major modifiable risk factors are hypertension and diabetes. The probable CVD risk with pre-hypertension and pre-diabetes, to some extent, is dependent on whether pre-HTN leads to hypertension and pre-DM leads to diabetes. Our aim was to study: the progression of prehypertension and prediabetes to overt hypertension and diabetes or to normal status, and the association of pre-obesity and obesity with prehypertension and prediabetes.
Methods: A total of 1200 patients equally distributed among three groups were studied for progression or regression. Group A included 400 patients of pre-hypertension, and group B included 400 patients of pre-diabetes and group C included 400 patients of pre-diabetes and pre-hypertension.
Results: Among the 400 studied patients with prediabetes 31 (7.8%) progressed to diabetes and only 9 (2.3%) progressed to hypertension over a period of two years. Patients with both prehypertension and prediabetes had a higher risk of progression to hypertension and diabetes (3% to hypertension and 15.5% to diabetes). Males were more prone to develop both pre-hypertension and pre-diabetes mellitus and progression. Obesity increased the risk of progression to hypertension and diabetes significantly.
Conclusions: The screening of people for pre-diabetes mellitus and pre-hypertension should be carried out at mass levels so as to diagnose them at an early stage and hence, their progression can be either halted or modified.

Keywords: Noncommunicable diseases, Prehypertension, Prediabetes, Cardiovascular diseases, Body mass index

INTRODUCTION

Non-communicable diseases (NCDs) have surpassed the communicable diseases as major cause of mortality and morbidity not only in the developed countries but in the developing countries as well.[1]

As per World Health Organization (WHO) report 2015 "By the year 2020, NCDs are expected to account for seven out of every ten deaths in the developing regions. Cardiovascular diseases account for most NCD deaths, or 17.5 million people annually.[2]

The major modifiable risk factors for development of cardiovascular disease are hypertension and diabetes. Hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke. In 2003, JNC-7 introduced a new category: pre-hypertension (pre-HTN) [BP of 120-139/80 to 89 mmHg].[3,4] Several national blood pressure surveys in the United States and other countries report that more than 30% of the general adult population has pre-HTN.[5,6]

JNC 7 on prevention, detection, evaluation and treatment of high blood pressure: normal: <120/80 mmHg, pre-

hypertension: 120–139/80–89 mmHg, hypertension: ≥140/90 mmHg, stage 1: 140–159/90–99 mmHg, and stage 2: ≥160/100.[7]

Similarly, ADA introduced the term pre-diabetes as a risk factor for overt diabetes and hence cardiovascular diseases. Impaired fasting plasma glucose (IFG) is associated with insulin resistance and an increased cardiovascular risk.

Although less risky than impaired glucose tolerance (IGT), IFG is coupled with a greater conversion from Pre-DM to overt diabetes (i.e. approximately 24% in less than three years) (Table 1).[8,9]

Table 1: Criteria for the diagnosis of prediabetes and diabetes.[8]

Variable	Prediabetes	Diabetes
Hemoglobin A_{1c} level, %	5.7–6.4	≥6.5
Fasting plasma glucose level		
mmol/l	5.6–6.9	≥7.0
mg/dl	100–125	≥126
Oral glucose tolerance test results*		
mmol/l	7.8–11.0	≥11.1#
mg/dl	140–199	≥200#
Random plasma glucose level		
mmol/l	-	≥11.1
mg/dl	-	≥200+

*2-hour plasma glucose level after a 75 g oral glucose tolerance test; # in the absence of unequivocal hyperglycemia, results should be confirmed by repeated testing; + only diagnostic in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis

The terminology of pre-hypertension, pre-diabetes was introduced with the concept that diabetes and hypertension being the major cardiovascular risk factors can be diagnosed at an early stage and hence, their progression can be either halted or modified.

Aims and objectives

The aims and objectives of the study were: to observe the progression of pre-hypertension and pre-diabetes to overt hypertension and diabetes or regression to normotensive and euglycaemic status; to see the basic clinical and biochemical parameters of patients of pre-hypertension, pre-diabetes and both; and to study the association of BMI, waist circumference and dyslipidemia with the progression of pre-hypertension and pre-diabetes.

METHODS

This prospective observational hospital-based study was conducted in the postgraduate department of medicine, Government Medical College Srinagar, over a period of 2 years, from January 2017 to December 2018.

Inclusion criteria

Age ≥18 years and individuals diagnosed as pre hypertension, prediabetic or both were included in the study.

Exclusion criteria

Known and newly diagnosed diabetes mellitus and hypertension patients and also pregnant women were excluded.

Study population

A total of 1200 patients were included in the study equally distributed among three groups. Group A included 400 patients of pre-hypertension, group B included 400 patients of pre-diabetes and group C included 400 patients of pre-diabetes and pre-hypertension. The work up of the patients included: relevant clinical history; self-reported information on socio-demographic and associated risk factor profile as a part of interview questionnaire; and general physical examination which included measurement of vitals, height, weight, waist circumference, systemic examination. Patients were classified on the basis of BMI as normal (BMI=18.5-22.9), overweight (BMI=23.0-24.9) and obese (BMI ≥25). Each participant was allowed a rest of at least 5-10 minutes before the first BP measurement. The average of the three measurements of blood pressure were used.

Fasting blood samples were taken to measure plasma lipids, glucose and HbA_1C. Fasting is defined as no caloric intake for at-least 8 hours. OGTT was performed by measuring 2-hour plasma glucose after a 75 g oral glucose load.

Statistical analysis

The recorded data was exported to data editor of statistical package for the social sciences (SPSS) version 20.0 (SPSS Inc., Chicago, Illinios, USA). Continuous variables were expressed as mean±SD and categorical variables were summarized as percentages. Chi-square test or Fishers exact test, whichever appropriate, was used for comparison of categorical variables. Graphically the data was presented by bar and pie diagrams. A p value of less than 0.05 was considered statistically significant. All p values were two tailed.

RESULTS

A total of 1200 patients in the study were equally distributed among three groups (Table 2). The number of patients increased as the age advanced with maximum number of patients in the age group of 50-64 years.

This was true for all three groups. Mean age of patients was 53.1±12.37 years. Mean age was 54.2±14.35, 51.7±10.83 and 52.7±11.29 in pre-hypertensive, pre-

diabetic and pre-hypertensive and pre-diabetic respectively (Figure 1).

Table 2: Total number of patients in all three study groups.

Group	No. of patients
Pre-diabetes	400
Pre HTN	400
Pre-diabetes + pre HTN	400
Total	1200

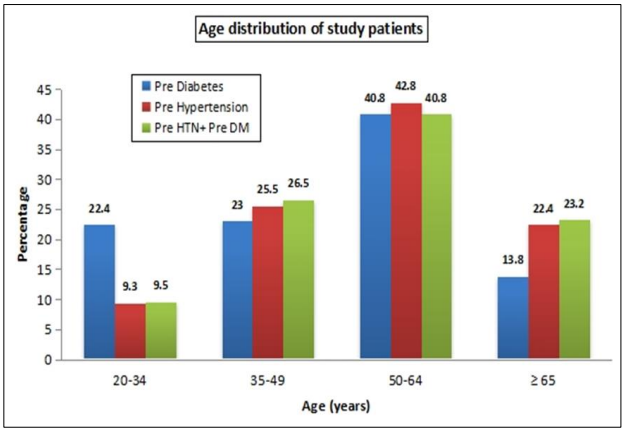

Figure 1: Age distribution of study patients.

Males outnumbered females in general except in pre-diabetic group where numbers were almost equal (Table 3).

Age had a significant impact on conversion rate of pre-diabetes to diabetes with patients of age ≥65 years having 6 times more likelihood of developing diabetes than patients in age group of 20-34 years (14.5% versus 2.2%) (Figure 2).

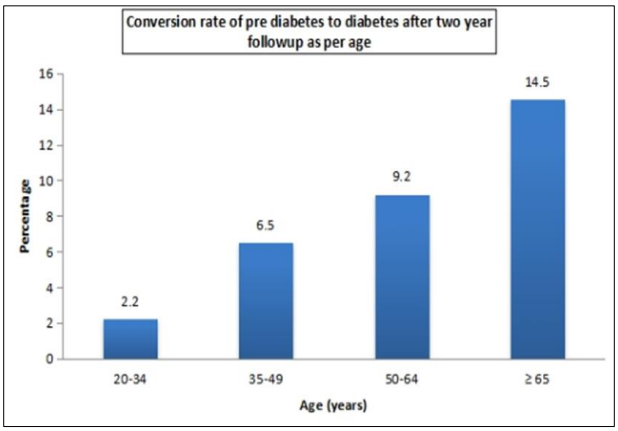

Figure 2: Impact of age on conversion rate of pre-diabetes to diabetes.

Low age was associated with higher conversion to euglycemia with 5.6% of patients within age group of 20-34 years reverting to euglycemia compared to 1.8% in the age group ≥65 years. There was an increase in conversion to hypertension with increase in age but the results were not statistically significant.

Age was a significant risk factor in determining the number of patients who developed diabetes from the group of patients who were having both pre-hypertension and pre-diabetes. Advancement of age was proportionately associated with increase in number of patients. Conversion rate was 7.9% in the age group of 20-34 years as compared to 23.7% in patients with age ≥65 years.

Lesser the age, more were chances of reverting to normoglycemia even with patients having both comorbidities (pre-hypertension and pre-diabetes). 5.3% in the age group of 20-34 years compared to 2.2% in the age group of ≥65 years.

Obesity has been strongly associated with conversion of pre-diabetes to diabetes mellitus with obese people (BMI ≥25 kg/m^2) having four times more chances of developing type 2 diabetes mellitus as compared to normal BMI (14.9% versus 3.7%) (Table 5).

Patients with normal BMI reverted to normoglycemia more often than obese patient (5.6% versus 1.7%). Patients with high BMI ≥25 kg/m^2 had significantly higher chances of developing hypertension from pre-hypertensive state than those with normal BMI (5.7% versus 1.3%). Conversion rate of patients with both comorbidities (pre-hypertension and pre-diabetes) to hypertension was significantly increased with increase in BMI. Conversion rate was 5.9% in patients with BMI ≥25 kg/m^2 as compared to 0.9% in patients with normal BMI. Obese patients (BMI ≥25 kg/m^2) had higher conversion rate to diabetes from pre-hypertension - pre-diabetes state than those with normal BMI (18.5-22.9 kg/m^2) (28.9% versus 4.6%) (Table 6).

Patients with normal BMI had more chances of reverting back to normoglycemic state as compared to those with high BMI (≥25 kg/m^2) (4.6% versus 2.2%). As the waist circumference of the patients increased the chances of developing diabetes increased manifolds (2.8% versus 7.4% versus 11.7%) with waist circumference of <94, 94-101 and >101 cm respectively (Table 7). Patients with low waist circumference (<94 cm) reverted to euglycemia more often than patients with high waist circumference (>101 cm) [5.7% versus 2.1%]. Conversion to hypertension from pre-hypertension was comparable in all three groups of waist circumference. More patients were converted to hypertension in the group with waist circumference >101 cm among the patients of pre-hypertension and pre-diabetes. Patients with waist circumference of >101 cm has 3-fold more chances of developing type 2 diabetes mellitus as compared to waist circumference of <94 cm among patients with pre-hypertension and pre-diabetes (23.4% versus 7.2%).

Table 3: Gender distribution of study patients.

Gender	Pre diabetes (%)	Pre hypertension (%)	Pre HTN+ pre DM (%)	Total (%)
Male	196 (49)	223 (55.8)	249 (62.2)	668 (55.7)
Female	204 (51)	177 (44.2)	151 (37.8)	532 (44.3)
Total	400	400	400	1200

Table 4: Observations and results summary.

Study groups	Pre-hypertension (%)	Prediabetic (%)	Prediabetic + pre-hypertension (%)	
Number	400	400	400	
Mean age	54.2±14.35	51.7±10.83	52.7±11.29	
Gender				
Males	196 (49)	223 (55.8)	249 (62.2)	
Females	204 (51)	177 (44.2)	151 (37.8)	
Progression to (average)				
Diabetes		31 (7.8)	62 (15.5)	
Hypertension	9 (2.3)		12 (3.0)	
Progression and BMI				
18.5-22.9	(p value=0.007) 0/117 (0)	(p value=0.002) 4/108 (3.7)	HTN (p value=0.045) 1/109 (0.9)	Diabetes (p value <0.001) 5/109 (4.6)
23-24.9	2/160 (1.3)	9/171 (5.3)	3/156 (1.9)	18/156 (11.5)
≥25	7/123 (5.7)	18/121 (14.9)	8/135 (5.9)	39/135 (28.9)
Waist circumference				
< 94	2/101 (2.0)	3/106 (2.8)	1/97 (1.0)	7/97 (7.2)
94-101	3/147 (2.0)	11/149 (7.4)	4/145 (2.8)	18/145 (12.4)
> 101	4/152 (2.6); p value=0.922	17/145 (11.7); p value=0.034	7/158 (4.4); p value=0.29	37/158 (23.4); p value=0.001)
IFG				
100-110		5/117 (4.3)	(p value=0.001)	
111-125		24/134 (17.9)		
IGT				
140-170		6/131 (4.6)	(p value=0.029)	
171-199		24/210 (11.4)		
Both IFG and IGT		34/208 (16.3) (p value=0.027)		
Triglycerides (≥200 mg/dl)	4/115 (3.5)	14/114 (12.3)		
Total cholesterol				
<200	(p value=0.744) 2/121 (1.7)	(p value=0.009) 4/117 (3.4)	HTN (p value=0.188) 1/114 (0.9)	DM (p value=0.024) 10/114 (8.8)
200-239	3/147 (2.0)	9/148 (6.1)	4/139 (2.9)	21/139 (15.1)
≥ 240	4/132 (3.0)	18/135 (13.3)	7/147 (4.8)	31/147 (21.1)

Table 5: Conversion rate of pre diabetes to diabetes after two-year follow up as per BMI.

BMI	Pre-diabetes	Diabetes	Percentage	P value
18.5-22.9	108	4	3.7	0.002*
23-24.9	171	9	5.3	
≥25	121	18	14.9	
Total	400	31	7.8	

Table 6: Conversion rate of pre HTN + pre DM to diabetes mellitus after two year follow up as per BMI.

BMI	Pre HTN + Pre DM	DM	Percentage	P value
18.5-22.9	109	5	4.6	<0.001*

Continued.

BMI	Pre HTN + Pre DM	DM	Percentage	P value
23-24.9	156	18	11.5	
≥25	135	39	28.9	
Total	400	62	15.5	

Table 7: Conversion rate of pre diabetes to diabetes after two-year follow up as per waist circumference.

Waist circumference	Pre diabetes	Diabetes	Percentage	P value
<94	106	3	2.8	0.034*
94-101	149	11	7.4	
>101	145	17	11.7	
Total	400	31	7.8	

Attainment of euglycemic state was more in patients with circumference <94 cm but results were not statistically significant (p value of 0.965). Patients with higher absolute values of fasting blood sugar had significantly higher chances of developing type 2 diabetes mellitus (17.9% versus 4.3%) when blood sugars of (111-125 mg/dl and 100-110 mg/dl) were compared. The conversion rate of patients to diabetes from pre-diabetes with IGT (171-199 mg/dl) was more than twice than patients with IGT (140-170 mg/dl) (11.4% versus 4.6%). When the both variables IFG and IGT were deranged the chances of developing diabetes increased significantly with a p value of 0.027. Patients with triglyceride level of ≥200 mg/dl had twice the chances of developing type 2 diabetes mellitus than with triglyceride <150 mg/dl (12.3% versus 5.7%). Even in case of pre-hypertension and pre-diabetes, hypertension conversion rate remained independent of triglyceride levels.

In patients of pre-hypertension and pre-diabetes mellitus, triglyceride levels remained a significant factor for determining conversion to diabetes after a two year follow up. Patients with triglyceride levels of ≥200 mg/dl had twice the chances of developing diabetes as compared to those with triglyceride levels lesser than 150 mg/dl (23.5% versus 10.2%). Patients with cholesterol level of >240 mg/dl had four times more chances of developing diabetes as compared to patients with cholesterol <200 mg/dl (13.3% versus 3.4%). Patients attaining euglycemic state had lesser level of cholesterol (<200 mg/dl) (p=0.653).

Those with both comorbidities (pre-hypertension and pre-diabetes mellitus), with cholesterol ≥240 mg/dl had higher chances of developing diabetes (4.8% versus 0.9%) as compared to patients with cholesterol <200 mg/dl. Patients with cholesterol ≥240 mg/dl had conversion rate of 21.1% as compared to 8.8% in those with cholesterol <200 mg/dl (p=0.024). Low level of HDL (<40 mg/dl) had six times more chances of developing diabetes as compared to patients with HDL (≥60 mg/dl) (13.3% versus 1.9%).

After two years of follow up maximum conversion to diabetes and hypertension was seen with the patients harbouring both comorbidities (prehypertension and pre-diabetes). Among 400 prehypertensive patients 9 (2.3%) patients converted to hypertension. Out of 400 prediabetic patients, 31 (7.8%) patients developed diabetes and 13 (3.3%) patients reverted back to normoglycemia. Among 400 patients who had both the comorbidities (pre-hypertension and pre-diabetes), 12 (3.0%) patients developed hypertension, 62 (15.5%) patients developed diabetes and 11 (2.8%) patients were reverted back to normoglycemic status.

DISCUSSION

NCDs are collectively responsible for almost 70% of all deaths worldwide.[10] The two major contributors i.e, HTN and DM are preceded by a latent phase named as pre-hypertension and pre-diabetes having variable course with good fraction of patients finally landing up having diabetes and hypertension. Studies conducted in the past included variable number of patients, however, the number of patients in our study were in approximation with Baltimore Longitudinal Study of aging, who had studied the natural history of progression from normal glucose tolerance to type 2 diabetes mellitus on 815 patients.[11]

The mean age of patients in our study was 53.1 (53.1±12.37) years which was in accordance with the study conducted by Nichols et al.[9] Gender distribution was equal in patients of pre-diabetes, whereas, in patients with history of pre-hypertension and in patients who had both pre-hypertension and pre-diabetes, males outnumbered females (55.8 versus 44.2 and 62.2 versus 37.8 respectively). Male gender being a risk factor for pre-hypertension has been established in many studies including the study conducted by Ganguly et al on Omani population.[12]

Prevalence of pre-hypertension and pre-diabetes increases with age. The proportion of patients who developed diabetes significantly increased from 2.2% in age group of 20-34 years to 14.5% in age group of more than 65 years (more than six-fold increase). The effect of age on prevalence of diabetes has been published in ADA bulletin where study was conducted on Bangladesh population by Akter et al.[13] Converse has been proved by our study among the patients who returned to euglycaemic status, most of them belong to younger age group. Similar trend was seen in patients with pre-hypertension and with the patients who had both pre-hypertension and pre-diabetes.

Among the 400 patients with pre-diabetes 31 (7.8%) of them progressed to diabetes and 13 (3.3%) of them reverted back to euglycaemic state. The conversion rate of pre-diabetes to diabetes has been estimated to as high as 90% in Chinese diabetes preventive trial, but the patients were followed over a period of 20 years. The annual progression of pre-diabetes to diabetes is 5-10%.[14,15]

The conversion rate of pre-hypertension to hypertension has been estimated to 69% over a period of 10 years by Chia et al.[16] Similarly, Vasan and colleges found conversion rate of 30% over 4 years.[17] The results of our study showed that among 400 patients studied, only 9 (2.3%) progressed to hypertension. It can be hypothesized that lifestyle and dietary measures are more effective in hypertension prevention than in diabetes which represents a chronic inflammatory state.

The observation of patients with both pre-hypertension and pre-diabetes revealed that a greater number of patients progressed to hypertension and diabetes (3% to hypertension and 15.5% to diabetes). Coexisting high blood pressure as a risk factor for progression to diabetes has been validated in a study by Yokota et al.[18] Not only do these coexisting diseases lead to early progression of hypertension and diabetes, but the patients with coexisting diseases are more prone to develop adverse cardiovascular outcomes early.[19]

The role of BMI in progression of pre-diabetes to diabetes or from pre-hypertension to hypertension can be stressed by the fact that not only did a greater number of patients with high BMI ($\geq$25 kg/m^2) progress to hypertension and diabetes mellitus (3.7% versus 7.8%) but also lesser revert to euglycaemic state. Similar results have been reflected by the comparative analysis of waist circumference of the studied patients. Patients with waist circumference of greater than 101 cm had fourfold increased risk of developing diabetes as compared to patients with waist circumference less than 94 cm (11.7% versus 2.8%). Similar changes were observed in patients having pre-hypertension and pre-diabetes progressing to hypertension (4.4% versus 1.0%) and diabetes (23.4% versus 7.2%). BMI and waist circumference as a predictor of progression to diabetes and hypertension has been validated in many studies.

The positive association between absolute values of blood glucose and progression to diabetes was observed in our study. Patients with higher fasting glucose levels (111-125) mg/dl had four times more chances of developing diabetes as compared to patients with blood glucose (100-110) mg/dl (17.9% versus 4.3%). Similar pattern was seen in patients with IGT, where patients with higher (171–199) mg/dl blood glucose levels progressed to diabetes significantly more often than with lower (140–170) mg/dl blood glucose levels [(11.4% versus 4.6%) (p value=0.029)]. In patients with both deranged parameters (IFG and IGT), the risk of progression to diabetes increased furthermore to 16.3% (p value=0.027). IGT with IFG as a marker of insulin secretory defect and suggestive parameter of pancreatic beta cell failure was demonstrated by Perreault et al in his study in 2001.[20] Furthermore, the higher levels of HbA1C (reflecting higher blood sugar levels) as a risk factor for progression to diabetes from pre-diabetes has been demonstrated by Zhang et al in his study published in Diabetes Care (2010).[21]

Triglycerides as a marker of insulin resistance and their role in identifying the insulin resistance state has been so strong that NCEPATP III guidelines incorporated triglycerides as one of the parameters in of metabolic syndrome. Our study also demonstrated a rising triglyceride level as a marker for progression to not only diabetes but also to hypertension. However, these values did not attain statistical significance, except in patients with both pre-hypertension and pre-diabetes who progressed to diabetes (p value=0.013). High cholesterol levels (>240 mg/dl) increased the risk of developing diabetes more than with lower levels of cholesterol (<200 mg/dl), 13.3% versus 3.4%, p value of 0.009. A positive correlation between triglyceride levels and HbA1C value has been shown by Naqvi et al in her study.[22] Similarly low HDL levels had its positive effect on progression of pre-diabetes to diabetes and patients with both pre-diabetes and pre-hypertension with HDL less than 40 mg/dl has significantly higher chances of developing hypertension in future years. These results have been earlier demonstrated by Gupta et al.[23]

Limitations

This study is an observational study and controlled study is required to understand the behaviour and the natural history of the subjects with prehypertension, prediabetes or both in comparison to normal subjects. No standard lifestyle or dietary modification protocol was designed for the study population to follow. Further follow up is needed to understand the long-term outcomes.

CONCLUSION

The study showed males were more prone to develop both pre-hypertension and pre-diabetes mellitus and have higher level of insulin resistance. Among the modifiable factors, obesity and the waist circumference are strongly associated with conversion to diabetes and hypertension, indicative of this very fact that life style modifications still forms the cornerstone for prevention and progression of both diabetes mellitus and hypertension. The biochemical parameters including high cholesterol and triglyceride and low levels of HDL can be indicative of progression to DM and hypertension. The off-shoots of this metabolic syndrome (pre-hypertension + pre-diabetes mellitus) reaching the liver is manifested by higher enzyme levels in these patients which finally culminate in NASH or CLD. The screening of people for pre-diabetes mellitus and pre-hypertension should be carried out at mass levels and masses should be simultaneously educated about monitoring and prevention of these risk factors which

result in the major burden of NCD and hence the economic loss.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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