Original Research Article

Assessment of serum prostate specific antigen level in type II diabetes mellitus

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ABSTRACT

Introduction: Diabetes mellitus (DM) refers to a group of common metabolic disorders with abnormal plasma glucose levels and disturbance in various metabolic pathways. Prostate specific antigen (PSA), a glycoprotein secreted by prostatic cylindrical cells and under the strong influence of androgens. Aim of the study was to compare serum PSA between diabetic and non-diabetic subjects and also correlate with Glycated hemoglobin (HbA1c), fasting blood sugar (FBS) and post prandial blood sugar (PPBS) in diabetic and non-diabetic subjects.

Materials and Methods: The present study was carried out in 85 diabetic subjects and 165 healthy controls in tertiary care hospital Surat. All the subjects were males categorized in different age and BMI and different duration of diabetes mellitus groups. Blood was collected and serum was analyzed for various biochemical parameters, fasting blood sugar, post prandial blood sugar by ERBA XL-640 fully auto analyzer, prostate specific antigen by e411 fully auto electrochemiluminescence (ECLIA) analyzer and Glycated hemoglobin HbA1c by high pressure liquid chromatography (HPLC) principle based BIO-RAD D10 analyzer by using whole blood. Student t test used to compare two groups and pearson correlation coefficient (r value) used for correlation and p value, $p<0.05$ as statistical significant and $p<0.001$ highly statistical significant used for statistical analysis.

Results and Discussion: A significant decrease ($p<0.001$ for all) in fasting and post prandial blood glucose and HbA1c in the diabetic subjects compared to healthy controls was observed. Serum concentration of prostate specific antigen was significantly low (0.53 ± 0.23 ng/ml) ($p<0.001$) in the diabetic subjects compared to healthy controls (0.84 ± 0.60 ng/ml). The concentration of serum PSA was observed to be significantly low ($p<0.001$) in the diabetic subjects with 6-10 years duration compared to those with 1-5 years duration.

Conclusion: Lower level of Prostate specific antigen was recorded in diabetic subjects compared to healthy controls, which was due to low level of insulin like growth factor 1(IGF-1) in long term diabetes which is attributed to decrease in insulin production. In diabetic patients there is a need of reduction of cut off value of prostate specific antigen after study done with more number of subjects.

1. Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders with abnormal plasma glucose levels and disturbance in various metabolic pathways. Incidence of diabetes increases with age, as most cases being diagnosed after the age of 40 years. This equates to a life time risk of developing diabetes of 1 in 10.[1] Type II diabetes is caused by a combination of genetic factors related to impaired insulin secretion and insulin resistance and environmental factors such as obesity, overeating, lack of exercise, and stress, as well as aging.[2]

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1.1. Prostate specific antigen and diabetes

Prostate specific antigen (PSA), a glycoprotein secreted by prostatic cylindrical cells and under the strong influence of androgens. Epidemiological studies clearly indicate that the risk of several types of cancer (including pancreas, liver, breast, colorectal, urinary tract, and female reproductive organs) are increased in diabetic patients. An inverse association between diabetes mellitus and prostate cancer was found by numerous epidemiological studies.[3] Many studies reported that men with diabetes are at a decreased risk for prostate cancer[4–6] and lower levels of prostate specific antigen, though this relationship is not true in all age groups.[7] In the study by Mariko Naito et al, an association between prostate specific antigen and BMI in diabetic patients was not clear or significant, and the mean of prostate specific antigen levels in diabetic males was clearly less than non-diabetic men in the 60 years and older age group. It was concluded that the levels of prostate specific antigen in the overweight group were higher than other weight groups and it was low est in the diabetic elderly.[8] Fukui et al[9] reported lower levels of prostate specific antigen in the diabetic men except for the age group of 40-49 years but study conducted by Ghasemi et al did not find such lower levels in diabetics.[1]

Khalid et al observed that men with Type II diabetes especially those with high HbA1c levels had lower prostate specific antigen levels than non-diabetic men.[10] They compared with the study by nutritional health and nutrition examination survey study,[11] which also reported a decrease in mean prostate specific antigen for men with Type II diabetes. Fukui et al observed similar pattern in 50-79 age old Japanese men.[9] A number of workers have observed a negative relationship between serum prostate specific antigen levels and Type II diabetes. The hypothesis that more severe forms of diabetes might be associated with a lower prostate specific antigen level was further corroborated by the inverse association of HbA1c measurements with prostate specific antigen levels.[10] Looking into the various inputs regarding the levels of prostate specific antigen in type II diabetes mellitus and lacunae of literature of such study involving local population the present study was taken up to assess the status of serum PSA in diabetes mellitus subjects and compare with healthy control.

2. Materials and Methods

Cross sectional, case-control study was conducted for 6 month period at tertiary care hospital in Surat, Gujarat, after obtaining necessary ethical clearance from the institutional ethical committee, letter no IEC/OUT/51, dated 25/02/2016. Diagnosis of diabetes mellitus has been made as per American diabetic association (ADA) and WHO guideline.[12] A total number of 85 diabetics and 165 controls between the age group of 35-65 or above years were included in this study, taking confidence intwas further corroborated by the inverse association of HbA1c measurements erval 95%, power of 80%, and ratio of group 2:1 sample size determined. Serum was collected, stored and estimated next day, serum fasting and post prandial blood sugar was estimated by Glucose oxidase peroxidase method in auto analyzer Erba XL640, Serum PSA and HbA1c was estimated by ECLIA (Electro chemiluminescence immunoassay) based Cobas e411 fully auto analyzer and HPLC (High performance liquid chromatography) respectively. Using height (meter) and weight (kg), BMI (kg/m) was calculated based on Asian adults.[13]

Male subjects has been included between the age group of 35 and 65 and above and diabetic subjects on oral hypoglycemic agents without insulin. Females, subjects with prostatic cancer and benign prostatic hypertrophy, undergone prostatectomy, with type-1 diabetes mellitus, with other known hormonal disorders, diabetic subjects who were on both insulin and other oral hypoglycemic agents and who were below the age of 35 has been excluded.

2.1. Statistical analysis

Statistical data analysis was done by using SPSS software. Student t test using two mean and standard deviation used to compare two groups and pearson test for correlation coefficient (r value) was used for correlation between two groups in present study and p value <0.05 was considered statistically significant and p value < 0.001 was considered to be highly statistically significant.

3. Results

In present study we had measured serum level of PSA, FBS, PPBS and HbA1c between diabetic and non-diabetic subjects, subjects has been divided by various age group and BMI wise. Following results were obtained from current study.

P value calculated by two sample t test using two mean and standard deviation.

Table 1 Gives the levels of fasting, post prandial blood sugar, serum prostate specific antigen. Both fasting and post prandial blood sugar levels were significantly ($p< 0.001$) high in the diabetic subjects compared to control subjects. The levels of HbA1c were significantly ($p< 0.001$) high in diabetic subjects compared to control subjects. Serum PSA level in diabetic subjects were lower than control subjects which was highly significant ($p<0.001$).

Table 2 gives the correlation of prostate specific antigen with fasting, post prandial blood sugar and HbA1c. A negative correlation of PSA with FBS, PPBS and HbA1c in diabetic subjects and significant positive correlation in control subjects was observed.

Table 1: Levels of fasting, Post prandial blood sugar, HbA1c and Prostate specific antigen in control and diabetes mellitus subjects

Parameter	Diabetic subjects (n=85)	Non diabetic subjects (n=165)	P value
Age (year)	52 ± 9.5	51 ± 9.7	0.98
BMI (kg/m^2)	26.6 ± 2.74	25.73 ± 2.38	0.013
FBS (mg/dl)	194 ± 88.12	93.76 ± 10.75	<0.0 0 1
PPBS (mg/dl)	256 ± 133.15	104 ± 14.26	<0.001
HbA1c (%)	9.54 ± 2.87	6.01 ± 0.50	<0.001
PSA (ng/ml)	0.53 ± 0.23	0.84 ± 0.60	<0.001

Table 2: Correlation of prostate specific antigen with fasting and postprandial blood sugar and HbA1c in diabetes and control subjects

Subjects	Parameter	PSA (ng/ml)	
		r value	p Value
Diabetic subjects (n=85)	**FBS (mg/dl)**	-.053	0.628
Control subjects (n=165)		0.167	<0.05
Diabetic subjects (n=85)	**PPBS (mg/dl)**	-0.067	0.542
Control subjects (n=165)		0.244	<0.01
Diabetic subjects (n=85)	**HbA1c** (%)	-0.125	0.253
Control subjects (n=165)		0.189	<0.05

P value calculated by two sample t test using two mean and standard deviation.

Table 3 gives the levels of fasting and post prandial blood sugar, prostate specific antigen and HbA1c in different age groups of healthy and diabetic subjects. A significant decrease in serum PSA level in diabetic subjects compared to control subjects was observed in all age groups and similar pattern was seen for RBS, PPBS and HbA1c.

Table 4 gives comparative levels of prostatic specific antigen in the subjects with different body mass index. PSA levels are decreased in 25-29.99 kg/m^2 and $\geq$ 30 kg/m^2 group which was highly significant and in other groups, PSA level was decrease d but not significant. An increasing pattern of PSA was observed in control subjects unlike in diabetic subjects.

Table 5 gives the levels of fasting and postprandial blood sugar, HbA1c and prostate specific antigen in diabetic subjects of history of different duration of diabetes. PSA level in subjects with 6-10 year duration of diabetes was significantly low compared to subjects with 1-5 year of duration of diabetes. FBS, PPBS and HbA1c level were decrease d in 6-10-year duration of diabetes compared to 1-5 year duration of diabetes but which was not significant.

4. Discussion

The present study was carried out in male type II diabetic mellitus subjects who had been afflicted with disease for period spanning from 1 to 10 years and belonged to different age groups from 35 to 65 and more years. All the subjects had been on hypoglycemic medications but not on insulin. Serum level of fasting and postprandial blood sugar in diabetic subjects and healthy controls was 194.0 $\pm$88.12, 93.76 $\pm$ 10.75 and 256.0 $\pm$133.15, 104 $\pm$ 14.26 mg/dl respectively. Diabetic subjects had significantly higher levels than that of controls (p<0.001). Percentage of HbA1c in diabetic subjects was 9.54 $\pm$ 2.87 compared to control subjects (6.01 $\pm$ 0.50%), which was highly significant (p<0.001). With reference to FBS, PPBS and HbA1c levels in the different age groups of diabetic subjects no particular pattern was observed but the levels in corresponding age groups of controls was significantly lower in all the three parameters. Similar observations were found regarding FBS, PPBS and HbA1 c concentration in the subject with different duration of diabetes. The pattern of FBS, PPBS and HbA1c in present study groups was as reported by many previous workers.[14,15]

Benign prostatic hyperplasia and Type-II diabetes mellitus are disparate entities but diabetes is found in both the genders whereas prostatic hyperplasia is specific to males. One similarity of both these diseases, but not a rule is that the increased prevalence in advanced age groups. Both the diseases seem to be sharing similar epidemiological features which are possibly connected common pathogenic pathway related to ageing and diet. Though, an association has been reported between diabetes and increased risk of several cancers but in case of prostatic cancer an inverse relationship is found between these two conditions possibly due to the result of metabolic and hormonal ablation associated with diabetes mellitus. A number of workers have found an inverse relationship between prostatic cancer and diabetes but some other workers did not observe such an association.[16] At present one cannot categorically deduce any definitive conclusion on the basis of available scientific data regarding this inverse relationship.[16]

The explanation for this association may be that in maturity onset diabetes, the obvious changes are mostly due to either decreased secretion or increased resistance of

Table 3: Serum fasting blood sugar, post prandial blood sugar, prostate specific antigen and HbA1c in different age groups subjects of diabetes and healthy controls

Parameter	Subjects	Age (years) 35-44	P value	45-54	P value	55-64	P value	≥65	P value
FBS (mg/dl)	Diabetic subjects	181.10 ± 70.64 n =19	< 0.01	212.40 ± 84.09 n=32	< 0.01	185.23 ± 84.37 n=26	< 0.01	186.25 ± 145.82 n =8	< 0.05
	Control subjects	91.83 ± 10.22 n =32		93.11 ± 11.95 n=50		96.14 ± 8.84 n=42		93.35 ± 11.85 n =15	
PPBS (mg/dl)	Diabetic subjects	243.68 ± 93.0 n =19	< 0.01	253.75 ± 106.48 n=32	< 0.01	253.62 ± 95.26 n=26	< 0.01	304.25 ± 323.67 n =8	< 0.05
	Control subjects	101.64 ± 13.0 n =36		101.83 ± 15.58 n=63		107 ± 12.58 n=49		109.53 ± 14.42 n=17	
HbA1C (%)	Diabetic subjects	9.88 ± 3.72 n =19	< 0.01	9.31 ± 2.13 n=32	< 0.01	9.45 ± 2.56 n=26	< 0.05	9.99 ± 4.31 n=8	< 0.01
	Control subjects	5.99 ± 0.39 n =35		5.94 ± 0.55 n=63		6.05 ± 0.50 n=49		6.21 ± 0.49 n=17	
PSA (ng/ml)	Diabetic subjects	0.44 ± 0.16 n =19	< 0.05	0.54 ± 0.22 n=32	< 0.05	0.61 ± 0.26 n=26	< 0.05	0.40 ± 0.29 n=8	< 0.01
	Control subjects	0.75 ± 0.51 n =36		0.74 ± 0.53 n=62		0.96 ± 0.68 n=45		1.14 ± 0.70 n=15	

P value calculated by two sample t test using two mean and standard deviation.

Table 4: Comparative levels of serum prostate specific antigen in diabetic and control subjects with different levels of Body mass index

Parameter	Subjects	BMI kg/m^2			
		< 23	23-24.99	25-29.99	≥30
PSA (ng/ml)	Diabetic Subjects	0.56 ± 0.29 n = 4	0.61 ± 0.22 n = 23	0.49 ± 0.23 n = 51	0.52 ± 0.17 n = 7
	Control subjects	0.69 ± 0.38 n = 17	0.82 ± 0.57 n = 52	0.83 ± 0.60 n = 82	1.77 ± 0.65 n = 6
	p Value	0.509	0.092	<0.0 0 1	<0.001

P value calculated by two sample t test using two mean and standard deviation.

Table 5: Correlation between duration of diabetes mellitus and fasting blood sugar, post prandial blood sugar, HbA1c and prostate specific antigen

	Duration of diabetes (years) and number of subjects		
Parameter	1-5 (56)	6-10 (29)	P value
FBS (mg/dl)	198.30 ± 93.56	187.70 ± 77.61	0.602
PPBS (mg/dl)	266.10 ± 146.60	237.20 ± 102.10	0.345
HbA1c (%)	9.59 ± 2.94	9.45 ± 2.77	0.832
PSA (ng/ml)	0.63 ± 0.21	0.33 ± 0.12	<0.001

P value calculated by two sample t test using two mean and standard deviation.

Table 6: Correlation coefficient (r value) of duration of Diabetes and Prostate specific antigen

		PSA (ng/ml)
Duration of diabetes (year)	Pearson correlation (r value)	-0.646
	p Value	< 0.001

P value calculated by using pearson test for correlation between two groups.

insulin response. Some researchers commented that role of various insulin like growth factors (IGF) and insulin resistance resulting into hyperinsulinaemia and pancreatic enlargement with the progress of diabetes mellitus. In diabetics the ability of pancreas to secrete insulin is compromised resulting into decrease d insulin secretion and low portal insulin, which decreases growth hormone and ultimately IGF-I from liver. IGF-I binds to the IGF-I receptor, a tyrosine kinase receptor that transduces signals to the nucleus and mitochondrion primarily via the mitogen-activated protein kinase (MAPK) and PI3K/Akt pathways.[17] IGF-I plays important role in understanding etiopathogenesis of prostate disease, to promote normal growth and cellular proliferation, which lead to increase in PSA level.

It is well known fact that prostate specific antigen is one of the most useful biomarkers for detection of enlargement of prostate in prostate cancer. Terner et al[18] and Xu et al[19] observed decreased risk of prostate cancer in diabetes. In the present study, prostate specific antigen level in the healthy controls was 0.84 ± 0.60 ng/ml compared to diabetic subjects 0.53 ± 0.23 ng/ml, which was significantly (p<0.001) higher than that present in diabetic subjects (Table 1). These levels were in correlation with the results (1.16 ± 0.22 ng/ml, 1.01 ± 0.22 ng/ml) by Khalid et al but both in healthy controls and diabetic subjects the levels of the present study were lower than reported by others.[10] Study conducted by Walner et al, Fukui et al, AL Ashadi et al and Osden C et al also reported decreased level of

PSA in diabetic subjects which was in correlation with our study.[9,20–22]

Study conducted by Ou X et al, Maudi et al and Sharma et al have found higher levels in diabetics compared to non-diabetics[23–25] which were unlike the results found in our study. Whereas study conducted by Burke JP et al did not find any relation between PSA level with diabetes.

A correlation between HbA1c and PSA values in both diabetic and non-diabetic subjects was observed in this study. A negative but insignificant correlation between HbA1c and PSA was observed in diabetic subjects (r = -0.12, *p* =0.253) whereas significantly positive correlation was observed in non-diabetic subjects (r=0.2, p= 0.05) (Table 2). This finding is similar to the findings reported by Khalid et al.[10] There is a negative correlation between serum PSA and HbA1c level in diabetes subjects which is in correlation with findings of Al-ashadi et al[21] and Fowke et al.[26]

From the data, inference can be drawn that Type-II diabetic subjects tend to have lower concentration of prostate specific antigen which may be due to disturbance in the concentration of insulin, and this disturbance in this concentration of this hormone may reflect on IGF, which has got influence on prostate gland. Study conducted by Betancourt et al explained that the reason for decreased PSA in diabetics is due to low level of IGF-1 in long term diabetes which is attributed to decrease in insulin production.[27]

In the present study, FBS, PPBS, HbA1c and PSA level also analyzed in different age groups such as 35-44-year,

45-54 year, 55-64 years and 65 or more years of both diabetic and healthy control subjects (Table 3). The pattern of the results was similar to that of total subjects of both controls and diabetic subjects. In present study, findings of PSA in diabetes was less age dependent compared to non-diabetic subjects. In diabetic subjects of the present study, PSA level increase d with age until 65 years after that a significant decrease in PSA level was seen, whereas in healthy controls an increased pattern of PSA with advancing age was observed, which was similar to findings reported by Al-ashadi et al.[21] This may be due to diminished capacity of prostate to produce PSA,[28] due to prostate ischemia resulting from local micro vascular complications associated with DM.[29] Study conducted by Cvitkovik I et al and Ainahi et al also reported similar pattern of results.[28–30]

In this study, BMI was calculated and segregated the subjects under categories i.e normal (<23 kg/m^2), mild obese (23 – 24.99 kg/m^2), moderate obese (25 – 29.99 kg/m^2) and severe obese ($\geq$30 kg/m^2). PSA level observed significantly lower in diabetics compared to non-diabetic subjects with BMI of 25 – 29.99kg/m 2 and $\geq$30 kg/m^2 obese subjects, but no such significant difference was observed in the subjects with mild obese and healthy subjects (Table 4). Khalid et al found a lower level of PSA in diabetics in obese compared to healthy controls. Our results were in correlation with that of the observations made by Khalid et al. Other researchers also found decreased concentration of serum prostate specific antigen with increasing BMI and these trends were significant among men younger than 60 years of age.

The findings of this study were in correlation with the results of other studies.[31,32] Liu et al[33] reported prostate specific antigen levels of 0.31ng/ml, 0.52ng/ml, 0.76 ng/ml, 1.11 ng/ml and 1.99 ng/ml in the subjects with BMI 20.3 kg/m^2, 23.4 kg/m^2, 25.4 kg/m^2, 27.5 kg/m^2 and 31 kg/m^2 respectively. They reported that subjects with BMI of $\geq$ 30kg/m^2 had high concentration of prostate specific antigen compared to other BMI groups. In the present study also, higher levels of prostate specific antigen in BMI of $\geq$30 kg/m^2 were obtained followed by other BMI groups of controls [0.69 ng/ml (<23 kg/m^2); 0.82 ng/ml (23-24.99 kg/m^2); 0.83 ng/ml (25-29.99 kg/m^2) and 1.77 ng/ml ($\geq$30 kg/m^2)]. Whereas in diabetics no such definitive pattern was observed, however the levels in controls were much higher than that of each corresponding BMI group of diabetics. Ghasemi et al[1] also investigated relation between diabetes and BMI with prostate specific antigen, but study was limited to 60-92 years of age only whereas our study age groups were between 35 and 65 years or more. Mean prostate specific antigen reported in diabetic and control subjects was 1.74 $\pm$ 2.48 ng/ml and 1.93 $\pm$ 3.13 ng/ml respectively and the mean BMI was 27.08 $\pm$ 3.84 kg/m^2, there was a significant difference between control and diabetic subjects but the levels of our study

were much below than that of reported by these workers though there was a significant difference between both the groups. Muller et al[18] found an association of diabetes mellitus and BMI with prostate specific antigen and reported lower prostate specific antigen concentration in diabetic subjects compared to non-diabetic s. They reported that the serum concentration of prostate specific antigen in diabetic subjects with different BMI <25 kg/m^2, 25-29.99 kg/m^2 and $\geq$ 30 kg/m^2 was 0.89 ng/ml, 0.85 ng/ml and 0.76 ng/ml) respectively, which was lower than that of the healthy controls. Similar pattern of results were also observed in the present study (Table 4). An inverse relation between PSA and BMI in diabetic and non-diabetic subjects was reported by Bonne et al[35], but in the present study no such relation was observed. In present study there was a positive correlation of PSA with BMI in non-diabetic subjects but in diabetic subjects, no specific pattern was observed. However, in diabetics compared to control, moderate and severe obese subjects had lower level of PSA. Lower level of PSA in the subjects with high BMI may be due to hemodilution or effects of testosterone on PSA level.

In the present study, out of a total of 85 diabetic subjects, we have categorized them into two groups based on the duration of the disease they were afflicted with. 56 subjects were of those who had Type-II diabetes mellitus from 1 to 5 years where as 29 subjects were those who had diabetes mellitus from 6 to 10 years. There was significantly lower level of PSA found in 6-10-years duration (0.33 $\pm$ 0.12 ng/ml) of diabetes compared to 1-5-year duration (0.63 $\pm$ 0.21 ng/ml) (p$<$0.001). Muller et al had also reported the levels of prostate specific antigen in diabetic subjects with duration of 0-5, 6-10 and $>$10 years. They reported 29.6% (0-5), 22.4 % (6-10) and 24% in 0-5, 6-10 and $>$10 respectively had lower concentrations when compared with non-diabetic subjects. The present study also showed similar pattern but unlike the above referred study, we have observed that as there was more increased in duration the more in the decrease in PSA levels. The mean prostate specific antigen of 1-5 years duration group was 40% lower than that of control subjects and mean prostate specific antigen of 6-10 years duration group was 63% lower than that of control group. In both the groups, the difference was highly significant (p $<$0.001) and we have also observed a significant (p$<$0.001) negative correlation of PSA with duration of diabetes which is in similar line of the observations reported by Muller et al (Table 6). Other workers also reported similar pattern in diabetic subjects of different duration of disease. The decreased pattern of serum PSA in diabetics with longer duration may be attributed to either decrease effectiveness or decreased levels of insulin like growth factor 1.[34] Molecular mechanism of IGF-I already explain above.

5. Conclusions

Lower level of Prostate specific antigen was observed in diabetic subjects compared to healthy controls. As the duration of diabetes increases there is a decrease in prostate specific antigen in serum. In diabetic patients there is a need of reduction of cut off value of prostate specific antigen after study done with more number of subjects. A significant negative correlation between duration of diabetes with serum prostate specific antigen concentration was observed. Significantly higher concentration of prostate specific antigen was found in healthy controls compared to diabetic subjects in BMI category of 25-29.99 kg/m^2 and $\geq$ 30 kg/m^2.

6. Strengths

This study was an elaborative study comprising of both diabetic subjects and healthy controls with different age, duration and BMI groups.

7. Limitations

In the present study number of diabetic subjects was low, especially subjects with $\geq$ 65 years of age group. Though we have done prostate specific antigen analysis but supportive diagnostic evidence in the form of radiological data was not obtained, to get information such as whether any person had benign prostatic hyperplasia or prostate cancer, though such subjects were excluded albeit on the basis of clinical history.

8. Acknowledgements

The institutional ethical committee of SMIMER medical college and hospital approved this study.

9. Conflict of interest

Author declare no conflict of interest.

10. Ethical standards

Ethical Committee approval for conduct of above mentioned study. Reference no. IEC/OUT/NO-51, dated-25/02/2016 by Office of the Ethics committee, Surat Municipal Institute of Medical Education and Research, Surat.

11. Research involving human participants and/or animals

This research involved human participant and research work was approved by institutional ethical committee of SMIMER, Surat.

12. Informed consent

Duly signed informed and written consent from all participants was obtained.

13. Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional ethical committee and/or national research committee.

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