www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v7i1.06

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Study of serum testosterone level in males with Prediabetes, before and after 3 months of metformin therapy, in patients attending a tertiary care hospital in West Bengal, Eastern India

Authors
Neeraj Sinha[1], Animesh Maiti[2*], Anirban Sinha[3], A K Basu[4], Tapas Chandra Das[5]
[1]Senior Resident, [2]Associate Professor, [3]Assistant Professor, [4]Professor and Head
Department of Endocrinology and Metabolism, Medical College, Kolkata
[5]Senior Resident, Department of Endocrinology and Metabolism, Medical College, Kolkata
*Corresponding Author
Dr Animesh Maiti
Associate Professor Department of Endocrinology and Metabolism Medical College, Kolkata, India

Abstract
Introduction: *Hypogonadism is common in diabetes and prediabetes both. Metformin ,insulin sensitiser, is approved therapy for prediabetes*
Aim of the study: *to assess whether metformin has any effect on serum testosterone level or not in males with prediabetes*
Materials and Methods: *48 males with prediabetes participated in the study .They were divided in two groups -Group A with baseline serum testosterone level more than 300 ng/dl and Group B with baseline serum testosterone level less than 300 ng/dl. Their testosterone levels were re-evaluated after 3 months of metformin therapy*
Result: *Prediabetes men in hypogonadal group showed significant improvement in serum testosterone level. Both groups participants had improvement in erectile dysfunction*
Conclusion: *metformin therapy in prediabetes male also helps in improvement of testosterone level*

Introduction

Prediabetes is defined by blood glucose concentrations higher than normal, but lower than established threshold for diagnosis of Diabetes[(1)]. The prevalence rates for prediabetes have been increasing steadily in the past few decades.

Association of hypogonadism with type 2 diabetes mellitus is increasingly being recognized[(2)]. Many studies show that insulin resistance is related inversely with serum testosterone level[(3,4,5)]. Hypogonadism has been found to be associated not only with diabetes but also with prediabetes and metabolic syndrome[(7,25)].

Metformin is drug of first choice for early type 2 diabetes mellitus and approved therapy for prediabetes.

Till date there are very few studies which have examined the effect of metformin on androgen levels in men[(7,8,9,10,11)]. So this study was planned to assess the effect of 3 months of metformin

therapy on men with prediabetes in respect to androgen level and erectile dysfunction.

Aims and Objectives`

Primary objective: To study serum testosterone level in males with prediabetes and compare the serum testosterone level of the same patient after 3 months of metformin 500 mg BD therapy.

Secondary objective: To study and compare the changes in body weight, insulin resistance, lipid profile and IIEF-5 scores for Erectile dysfunction after 3 months of metformin therapy

Materials and Methods

The study consist of a longitudinal, prospective, interventional case series analysis of men with prediabetes. This is a single centre study carried out in the department of Endocrinology and metabolism, Medical College, Kolkata with the study duration being February 2016 to July 2017.

Inclusion Criteria

1) Prediabetes Men with age 18- 60 years

Prediabetes was diagnosed if any of the following criteria were met:

a) Fasting plasma glucose 100-125 mg/dL (IFG),

b) two-hour OGTT 140-199 mg/dL (IPG), or

c) HbA1c 5.7%-6.4%.

The definition is adopted from the recommendations of the ADA.

Diabetes was diagnosed if the patient hada prior history of diabetes or if the glycemic variables reached the criteria of diabetes: fasting glucose ≥126 mg/dL, two-hour OGTT glucose ≥200 mg/dL, or HbA1c ≥6.5%

Exclusion Criteria

-Prediabetes males who were already on oral hypoglycemic agents including metformin

-Patient with diabetes mellitus, or glycemic variable reached criteria of diabetes

-Patient of known hypogonadism (eg. Klinefelelter syndrome, kallmann syndrome, multiple pituitary hormone deficiency, either testicular volume less than 12 ml) or receiving testosterone replacement therapy

-patients with hypothyroidism or hyperthyroidism, acromegaly, cushing syndrome

- patients on steroids in any form , or history of taking steroid with prednisolone equivalent 7.5 mg /day in last 3 months.

-Patient taking drugs which are known to interfere with testosterone level eg. cytotoxic chemotherapy, ketoconazole, antiandrogens, 5 alpha reductase inhibitor ,heroin, methadone

-H/O tumour, radiation, head trauma

-Any other chronic disease such as Kidney disease, cirrhosis of liver, chronic heart failure, psychiatric disease

The study was conducted after obtaining clearance from the Institutional Ethics Committee of Medical College, Kolkata.

Informed consents were taken from all the subjects involved in the study

Study Protocol

All male patients with blood glucose level in prediabetes range were advised lifestyle modification in terms of individualised reduction in calorie intake and exercise 30 minutes per day. All were asked to report after one month of this. Only those whose blood sugar persisted in prediabetes range were included in the study; those who became euglycemic or those whose blood sugar met the diagnostic criteria for diabetes were excluded from the study. History and physical examination was done as per prespecified proforma. Enquiry was specially made for the erectile function of penis and patients were asked their responses as per IIEF-5 questionnaire for erectile dysfunction. Blood samples for biochemical and hormonal assays taken. Patients were advised to continue lifestyle improvement measures and to take metformin 500 mg twice a day and report to diabetes OPD monthly.. Re-assessment of the patients-in terms of history, IIEF-5 score, physical examination, biochemical and hormonal blood tests were done.

For analysis, patients were divided in two groups- Group A and Group B. Group A had baseline serum testosterone level > 300 ng/dl and was

considered eugonadal, and Group B had baseline serum testosterone level less than 300 ng/dl and was considered hypogonadal. This is as per recommendation of Endocrine society[12]. Also most previous studies have taken serum testosterone value of 300 ng/dl to differentiate hypogonadism and eugonadism in adult males.[7]

Physical examination included anthropometric data i.e weight, height, BMI, waist circumference, hip circumference. Blood Pressure was measured in the non dominant arm, in sitting position and after a 5-minute rest, using a standardized mercury sphygmomanometer.

Acanthosis nigricans (grade 0 to 4) were assessed. [13]

Insulin resistance: Assessed by Homeostasis model assessment (HOMA-IR).

HOMA IR = [Fasting insulin (µU/ml) x Fasting glucose(mg/dl)] / 405

IIEF-5 SCORE for erectile dysfunction was noted [14]

The International Index of Erectile Function (IIEF-5) Questionnaire

The International Index of Erectile Function (IIEF-5) Questionnaire

Over the past 6 months:					
1. How do you rate your **confidence** that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, **how often** were your erections hard enough for penetration?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
3. During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time)4	Almost always/always 5
4. During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, **how often** was it satisfactory for you?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
IIEF-5 scoring: The IIEF-5 score is the sum of the ordinal responses to the 5 items. 22-25: No erectile dysfunction 17-21: Mild erectile dysfunction 12-16: Mild to moderate erectile dysfunction 8-11: Moderate erectile dysfunction 5-7: Severe erectile dysfunction					

History, physical examination and biochemical and hormonal assays were repeated after 3 months of metformin therapy.

Methods of Endocrine and Metabolic Biochemical Parameters assessment:

Serum Total Testosterone:

Total testosterone is measured as IMMULITE/ IMMULITE 1000 Testosterone,

a solid-phase, enzyme-labeled, competitive chemiluminescent immuno assay in automated IMMULITE 1000 analyzer.

Free testosterone was calculated from the total testosterone, SHBG, and albumin levels with vermeulen formula.

Serum SHBG: solid phase chemiluminescene enzyme immunometric assay in automated IMMULITE 1000 analyser (siemens)

Serum LH ,FSH , TSH ,INSULIN were measured by solid phase, two site chemiluminescent immunometric assay in automated IMMULITE 1000 analyzer using Siemens kit.

Statistical methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ±SD and results on categorical measurements are presented in Number (%). Significance is assessed at a level of 5%.

Normality of data was tested by simultaneous Anderson Darling test, Shapiro-Wilk test and graphically by QQ plot.

Paired t-test or Wilcoxon Signed Rank test was applied to detect any significance change of study parameters measured on two occasions for same group of patients. A p value of <0.05 was considered as statistically significant.

Statistical software: The Statistical software namely SAS (Statistical Analysis System) version 9.2 for windows, SAS Institute Inc. Cary, NC, USA and Statistical Package for Social Sciences (SPSS Complex Samples) Version 21.0 for windows, SPSS, Inc., Chicago, IL, USA were used for the analysis of the data. Microsoft word 2010 and Microsoft Excel 2010 (Microsoft Corp, Redmond, WA, USA), have been used to generate graphs and tables.

Observations and Results

Patient Selection

A total of 104 male patients came with blood sugar in prediabetes range. 38 were excluded from the study as they met exclusion criteria. 3 did not consent to participate in the study. 15 were lost to follow up and didn't report after 3 months of metformin therapy. So a total of 48 prediabetes male completed the study.

Result

Table 1: Results of participants, before and after 3 months of metformin 1000mg/d

		N	Mean	Std. Deviation	p
Pair 1	Weight-baseline	48	79.75	12.175	<0.001
	Weight -follow-up	48	78.23	11.134	
Pair 2	BMI-baseline	48	28.48	4.390	<0.001
	BMI-follow-up	48	27.92	3.956	
Pair 3	WC-baseline	48	97.44	7.128	<0.001
	WC-follow-up	48	96.02	6.279	
Pair 4	systolic BP-baseline	48	129.42	8.887	0.057
	systolic BP-follow-up	48	127.17	7.617	
Pair 5	Diastolic BP-baseline	48	84.13	4.256	0.069
	Diastolic BP-follow-up	48	83.00	3.620	
Pair 6	FPG-baseline	48	105.83	10.263	<0.001
	FPG-follow-up	48	94.25	11.226	
Pair 7	PPPG-baseline	48	163.50	14.791	<0.001
	PPPG-follow-up	48	141.88	17.688	
Pair 8	HbA1C-baseline	48	5.98	.124	<0.001
	HbA1C-follow-up	48	5.57	.519	
Pair 9	Fasting Insulin Level-baseline	48	12.15	4.934	<0.001
	Fasting Insulin Level-follow-up	48	10.56	3.672	
Pair 10	HOMA -IR-baseline	48	3.17	1.374	<0.001
	HOMA -IR-follow-up	48	2.56	.965	
Pair 11	Total cholesterol-baseline	48	183.73	35.707	0.010
	Total cholesterol-follow-up	48	175.73	27.945	
Pair 12	LDL-baseline	48	103.81	21.027	0.189
	LDL-follow-up	48	101.13	16.217	
Pair 13	HDL-baseline	48	40.06	6.155	0.002
	HDL-follow-up	48	41.69	6.261	
Pair 14	TG-baseline	48	178.92	71.125	0.003
	TG-follow-up	48	153.46	30.947	
Pair 15	e-GFR-baseline	48	88.54	12.810	0.888
	e GFR-follow-up	48	88.83	11.329	
Pair 16	Total Testosterone-baseline	48	377.96	141.607	0.005

	Total Testosterone-follow-up	48	410.65	116.694	
Pair 17	LH-baseline	48	3.54	.651	0.212
	LH-follow-up	48	3.69	.657	
Pair 18	FSH-baseline	48	3.90	.555	0.864
	FSH-follow-up	48	3.92	.539	
Pair 19	SHBG-baseline	48	20.33	11.434	0.015
	SHBG-follow-up	48	21.17	12.893	
Pair 20	Free Testosterone-baseline	48	10.10	3.827	0.017
	Free Testosterone-Follow-up	48	10.83	3.027	

After 3 months of metformin therapy patients with prediabetes had significant change in body weight, waist circumfrance, FPG, PPPG, HbA1C, HOMA IR, and total and free testosterone level. HDL, TG, SHBG also had significant changes. There was no significant changes in LDL, e GFR, LH, FSH and blood pressure.

A Comparison of study parameters was made in both the groups –group A (EUGONADAL) and group B (HYPOGONADAL)

Table 2: Comparison of study parameters in both groups

	Testosterone > 300,N=30				Testosterone < 300,N=18				
	Baseline		Follow-up		Baseline		Follow-up		p
Study Parameters	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**	
Weight	76.80	12.344	75.50	11.581	84.67	10.437	82.78	8.882	0.031
BMI	27.77	4.576	27.37	4.303	29.67	3.896	28.83	3.204	0.001
WC	96.17	7.188	95.00	6.868	99.56	6.688	97.72	4.860	0.044
Systolic BP	128.47	8.939	126.93	8.497	131.00	8.818	127.56	6.080	<0.001
Diastolic BP	83.93	4.533	83.20	4.089	84.44	3.854	82.67	2.744	0.002
FBS	105.47	10.119	94.33	7.988	106.44	10.766	94.11	15.476	0.106
PPBS	162.33	14.859	139.40	19.283	165.44	14.893	146.00	14.209	0.239
HbA1C	5.96	0.001	5.57	.547	6.01	0.001	5.57	.485	0.897
Fasting Insulin	11.00	4.323	10.00	3.384	14.06	5.407	11.50	4.033	<0.001
HOMA-IR	2.83	1.206	2.40	.855	3.72	1.487	2.83	1.098	<0.001
Total cholesterol	186.07	37.774	179.10	32.178	179.83	32.636	170.11	18.420	0.078
LDL	106.00	23.343	103.33	18.540	100.17	16.443	97.44	10.853	0.098
HDL	41.47	6.976	42.27	6.772	37.72	3.528	40.72	5.345	0.046
TG	169.37	54.701	155.70	31.735	194.83	91.937	149.72	30.103	<0.001
Creatinine	1.00	0.097	0.93	0.089	1.00	0.012	0.72	0.838	0.068
e-GFR	89.63	13.330	89.20	11.481	86.72	12.038	88.22	11.374	0.041
Total Testosterone	444.07	141.555	458.90	120.504	267.78	26.291	330.22	43.812	0.032
LH	3.43	.679	3.60	.724	3.72	.575	3.83	.514	0.561
FSH	3.97	.490	3.90	.607	3.78	.647	3.94	.416	0.435
SHBG	25.10	12.135	26.20	14.080	12.39	1.819	12.78	1.478	0.678
Albumin	4.00	0.032	4.00	0.001	4.00	0.035	4.06	.236	0.964
Free Testosterone	11.17	4.465	11.27	3.629	8.33	1.085	10.11	1.410	0.025
ED SCORE	18.23	5.500	19.13	4.932	18.06	4.659	19.18	3.746	0.201

P<0.05 considered as statistically significant, p computed by two-way repeated measure analysis by creating an interaction term on two factors: group = testosterone level below and above 300 and treatment= metformin

There is statistically significant change in weight, HOMA IR systolic and diastolic BP,HDL and TG in group B (baseline testosterone <300 ng/dl) than in group A (Baseline testosterone >300 ng/dl) While there is no statistical difference in change in SHBG in between both groups (P=0.678), there is a significant change in total testosterone (p=0.032) as well as free testosterone (p=0.025),more in group B than in group A .Both groups showed similar effect on ED score.

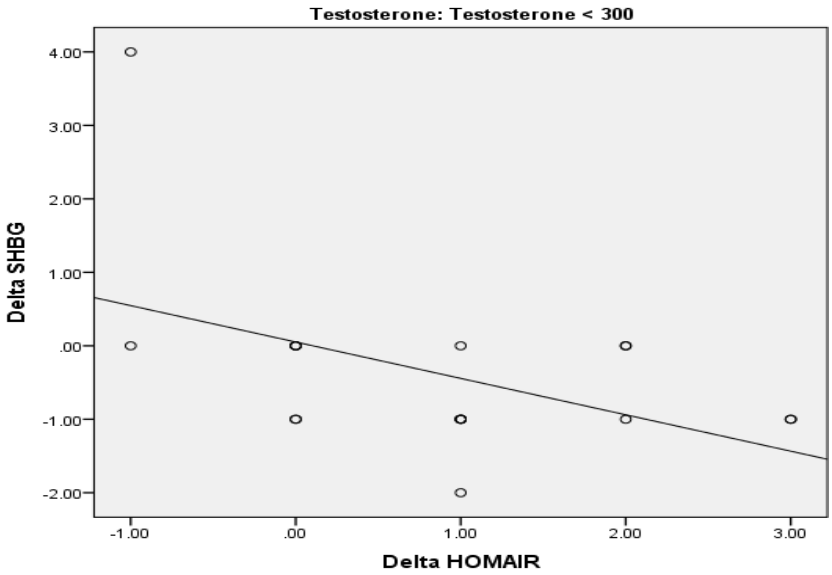
Change in testosterone had significant correlation with change in SHBG, while there was no significant relation with change in weight or change in HOMA IR.

Correlation			DELTA WT	DELTA SHBG	DELTA HOMAIR
Spearman's rho	DELTA TESTOSTERONE	Correlation Coefficient	-.191	.288*	-.182
		Sig. (2-tailed)	.194	.047	.216

This correlation was significant in hypogonadal group while the correlation was non significant in eugonadal group.

There was a significant negative correlation of change in SHBG with change in HOMA IR in hypogonadal group.

	Testosterone Level			Delta HOMAIR
Spearman's rho	Testosterone > 300	Delta SHBG	Correlation Coefficient	-.135
			p. (2-tailed)	.476
			N	30
	Testosterone < 300	Delta SHBG	Correlation Coefficient	-.427
			p. (2-tailed)	.048
			N	18



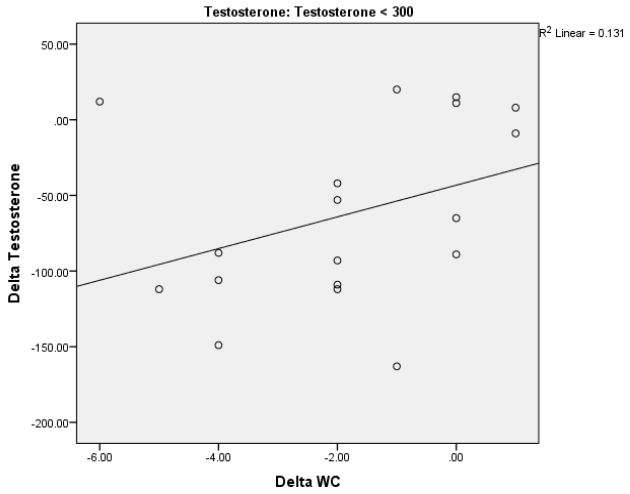
Apart from SHBG, there were significant negative correlations of change in both total and free testosterone with change in waist circumference, FPG and PPPG in the hypogonadal group while no such correlations were found in eugonadal group. There was no correlations with change in HbA1C in either group.

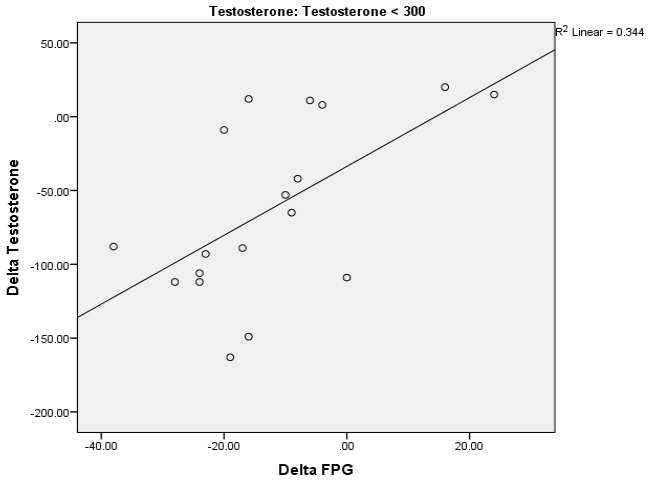
Correlations

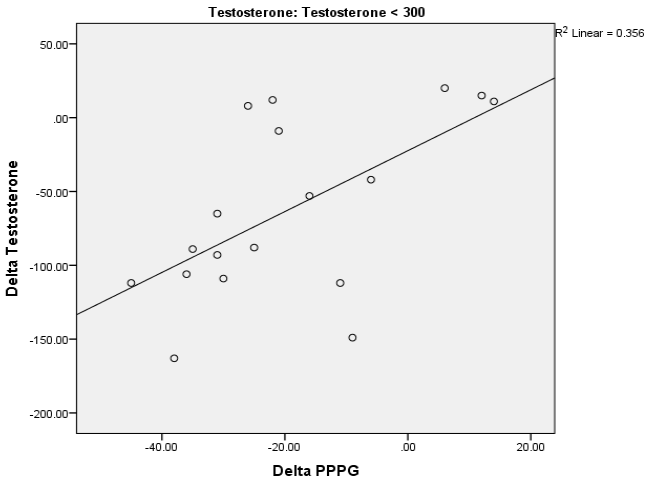
Testosterone				Delta WC	Delta FPG	Delta PPG	Delta A1C
Spearman's rho	Testosterone > 300	Delta Testosterone	Correlation Coefficient	.047	.166	-.157	.257
			p. (2-tailed)	.804	.382	.407	.171
			N	30	30	30	30
		Delta Free Testosterone	Correlation Coefficient	.049	.064	-.169	.209
			p. (2-tailed)	.799	.738	.372	.268
			N	30	30	30	30
	Testosterone < 300	Delta Testosterone	Correlation Coefficient	.401	.597**	.595**	-.159
			p. (2-tailed)	.049	.009	.009	.528
			N	18	18	18	18
		Delta Free Testosterone	Correlation Coefficient	.501*	.480*	.576*	-.150
			p. (2-tailed)	.034	.044	.012	.553
			N	18	18	18	18

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).



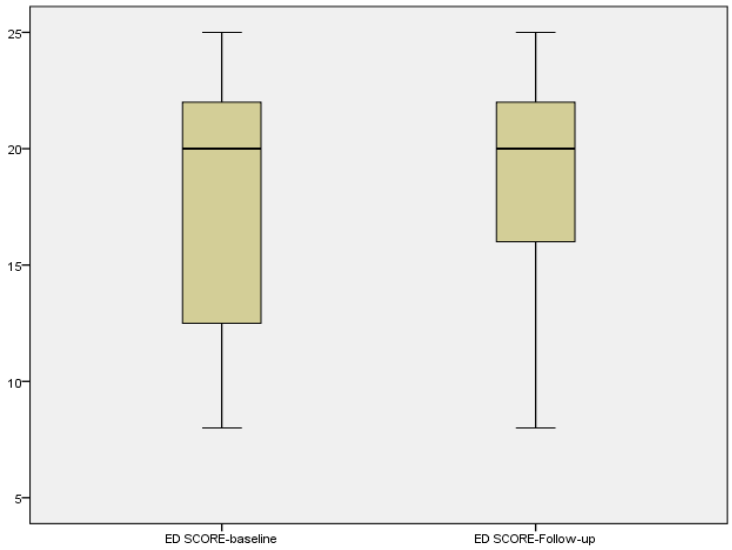




As regards to ED (erectile dysfunction) 13 patients in Group A had IIEF-5 score 16 or less indicating mild to moderate (or severe) erectile dysfunction. After 3 months of metformin therapy, 9 of them were still having mild to moderate erectile dysfunction while 4 of them had improved IIEF-5 scores (30.7%) .

In Group B, 8 patients had IIEF-5 score 16 or less and thus had mild to moderate (or severe) erectile dysfunction and after 3 months of metformin therapy , 4 of them were still in that category while other 4 had improved IIEF -5 scores.

There was improvement in mean IIEF-5 score in both the groups.



Group		Mean	Std. Deviation	Median (IQR)	p
Testosterone > 300	ED SCORE-baseline	18.23	5.500	22 (12-23)	0.049
	ED SCORE-Follow-up	19.13	4.932	23 (14-24)	
Testosterone < 300	ED SCORE-baseline	17.88	4.742	20 (12.75 - 22)	0.048
	ED SCORE-Follow-up	19.38	3.746	20 16.5 - 22)	

There was no statistical significant difference in change in mean IIEF-5 score in both the groups.

Discussion

In the present study, prediabetes patients after 3 months of metformin therapy were found to have a significant increase in both total and free testosterone. This increase was significant in hypogonadal group (Group B) and non-significant in eugonadal group (Group A). Significant changes in SHBG was observed in group B was seen. No changes in LH, or FSH level was observed.

After treatment, the increase in androgen level was accompanied by a significant reduction in body weight, BMI and waist circumference, in both groups and the reduction was more in hypogonadal group than in eugonadal group. Also, a more pronounced reduction in fasting insulin levels and HOMA IR was found in the hypogonadal group when compared with the eugonadal group (p value <0.001)

The relationship between adiposity, hyperinsulinemia and androgen secretion have been widely investigated. But the pathophysiological mechanisms involved in this clinical associations are not completely understood. It is understood that obesity is associated with insulin resistance and athis leada to a compensatory increase in insulin levels[15]. The excess circulating insulin and/or insulin resistance may affect testicular function. In this context, insulin receptors have been identified in Leydig cells[16], and insulin has been shown to acutely stimulate in vitro testosterone secretion by these cells [16,17].

Pitteloud et al[18] in their study demonstrated a significant correlation between insulin sensitivity and hCG stimulated testosterone production, suggesting that insulin resistance may play a causative role on the impairment of testicular steroidogenesis in men with metabolic syndrome.

As expected, in the present study, the therapeutic intervention resulted in a reduction of insulin level and HOMA IR in both groups. Metformin restores the enzymatic systems involved in the intracellular signalling cascade, increasing the tyrokinase activity of insulin receptor, among other effects[19,20] Therefore, metformin increases insulin sensitivity in peripheral tissues, particularly in liver, resulting in reduction of insulin level[20].

In this study, the change in testosterone correlated with change in SHBG. While there was a significant change in HOMA IR and body weight, they did not correlate with change in testosterone level .This can be because of the small sample size . Although change in testosterone correlated with SHBG and not with HOMA IR, change in SHBG had significant negative correlation with HOMA IR. This finding is in agreement with earlier studies.

Sex hormone binding globulin (SHBG) is the principal transportprotein for testosterone and oestradiol. Recent research however suggests that SHBG has additional biological significance. Low SHBG concentrations are associated with an increased risk of development of type 2 diabetes mellitus (DM)[21]. It has been proposed that the association is causal[22,23] and mediated by effectson insulin resistance.

While the study ‘effect of metformin and short term lifestyle modification on the improvement of male hypogonadism associated with metabolic syndrome by CASULARI et al[24] found significant increase in testosterone levels in both hypogonadal and eugonadal group ,our study suggests the benefit in hypogonadal group mainly.

Hypogonadism in T2DM have been found to be associated with hypogonadotropism or hypergonadotropism. However, in our study

hypogonadism was associated with eugonadotropism and there was no significant change in LH or FSH level after 3 months of metformin therapy. This may be because of multiplicity of mechanisms involved in hypogonadism. Also as patients were prediabetic and not having frank diabetes mellitus, no single mechanism could have dominated and so no definite pattern of hypergonadotropic or hypogonadotropic could be seen.

Participants of group B had a significant rise in testosterone which can be partly explained by change in SHBG, both showing positive correlation. SHBG in this group also correlated negatively with change in HOMA IR. Rise in testosterone was associated with significant weight loss, and decrease in HOMA IR.

Apart from androgens and other biochemical evaluations ,participants were also enquired about penile erectile function, both before and after 3 months of metformin therapy .Participants were asked regarding erectile function as per IIEF-5 score[58]. IIEF-5 is the sum of ordinal response to 5 items

IIEF-5 Score	Grade of erectile dysfunction
5-7	Severe
8-11	moderate
12-16	Mild to moderate
17-21	mild
22-25	No erectile dysfunction

Out of the 48 participants, 21 patients had IIEF-5 score of 16 or less than that, putting them into category of mild to moderate (or severe) erectile dysfunction. Although this is a tertiary care hospital finding, yet it shows how common erectile dysfunction is prevalent in prediabetes men. Prevalence of ED was similar in both eugonadal and hypogonadal group. In Group A (Baseline testosterone>300 ng/dl) 13 participants had IIEF-5 score 16 or less. After 3 months of metformin therapy, 9 of them were still having mild to moderate erectile dysfunction while 4 of them have improved IIEF-5 scores to more than 16.

In Group B, 8 patients had IIEF-5 score 16 or less and thus had mild to moderate (or severe) erectile dysfunction and after 3 months of metformin therapy, 4 of them were still in that category while other 4 had improved IIEF -5 score to more than 16.

The improvement was seen mostly in participants with ED of less than 6 months duration while those whose ED was of longer duration, metformin was mostly not effective.

Statistically there was no difference in response rate in group A and group B (Baseline testosterone level more than 300 ng/dl and less than 300 ng/dl, respectively). Also, improvement in ED was seen in most case within first month of therapy.

Insulin resistance has been found to be a major risk factor for E. In a state of insulin resistance, basal levels of serum insulin are elevated. This elevation of insulin disrupts the erectile function process by reducing NO bioavailability and promotion of atherogenicity[26,27]

Insulin resistance induces a state of NO deficiency. This occurs due to increased oxidative degradation and reduced NO synthesis. NO synthase is inhibited by asymmetric dimethylarginine (ADMA)[28], which is found in higher concentrations in individuals with insulin resistance

Animal studies on endothelium-dependent vasodilatation Kim et al., demonstrated that obese, insulin-resistant rats fed a high fat diet compared to controls had suppressed mRNA expression of NO synthase[29]. Treatment with metformin 300 mg/kg/day restored transcription of endothelial NO synthase in the penile tissue of obese rats as well as resolved insulin resistance. Prasad V .J et al also found that metformin improves vascular function in insulin resistant rats, independent of metabolic actions of metformin[32]. Clinical studies on endothelium-dependent vasodilatation Vitale et al., studied endothelial function in 65 patients with metabolic syndrome who were randomized to metformin 500 mg BID or placebo for 3 months[30]. Patients who received metformin demonstrated significantly improved endothelium dependent vasodilatation compared to placebo. The improvement in endothelial function was

associated with an improvement in insulin resistance. Knoblovits P, et al also found in their study that Metformin improves erectile function in nondiabetic patients with insulin resistance and erectile dysfunction[31].

Hence it can be said that improvement in erectile dysfunction in our participants which was similar in both eugonadal and hypogonadal group (p= 0.201), may have been mediated by improved endothelial function , although we could not measure endothelial dependent vasodilation.

Limitations of study

1) Small sample size
2) Control not taken
3) Endothelial dependent vasodilation was not measured
4) Hospital based study

Conclusion

Prevalence of hypogonadism in type 2 diabetes mellitus is high. This was also found in the study "late onset hypogonadism in type 2 diabetic and nondiabetic male: a comparative study "from Kolkata, India by Professor Dr A K Basu[2]. This study evaluated the effects of metformin on serum testosterone levels in prediabetes male population.

3 months of metformin therapy resulted in significant reduction in plasma glucose levels, body weight and HOMA IR. Low androgen level is common, not only in diabetes mellitus but also in prediabetes. Testosterone therapy for hypogonadism in diabetes also improves insulin sensitivity. However, metformin ,an insulin sensitiser, can also be useful in improving androgen level in men with prediabetes; and hence, this gives another reason for early institution of metformin in prediabetes, especially if patient is not able to follow lifestyle modifications. Erectile dysfunction is common in prediabetes also, and very early cases may respond with metformin.

Bibliography

1. RSSDI Textbook of Diabetes mellitus 3rd edition p 118-119
2. Asish Kumar Basu, P. Singhania, late onset hypogonadism in type 2 DM and non diabetic, J clin med assoc 2012, 110: 573-5
3. Kapoor D, Aldred H, Clark S, Channer KS, Jones TH (2007) Clinicaland biochemical assessment of hypogonadism in men with type 2diabetes: correlations with bioavailable testosterone and visceral adiposity.
4. Diabetes Care 30: 911-917. doi:10.2337/dc06-1426.PubMed: 17392552.
5. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A etal. (2004) Frequent occurrence of hypogonad-otropic hypogonadism in type 2 diabetes. J ClinEndocrinolMetab 89: 5462-5468. doi:10.1210/jc.2004-0804. PubMed: 15531498.
6. Grossmann M, Thomas MC, Panagiotopoulos S, Sharpe K, MacisaacRJ et al. (2008) Low testosterone levels are common and associated with insulin resistance in men with diabetes. J ClinEndocrinol Metab93: 1834- 1840. doi:10.1210/jc.2007-2177
7. Caldas ADA, Porto AL , Motta LDC, Casulari LA. Relationship between insulin and hypogonadism in men with metabolic syndrome. Arq Bras Endocrinol Metab 2009 ;53:1005-11
8. Ozata M , Oktenli C , Bingol N , Ozdemir IC. The effects of metformin and diet on plasma testosterone and leptin levels in obese men. Obes Res2001:9:662-7
9. Shegem NS,Nasir AM,Jbour AK, Batieha AM.EL –Shanti H ,Ajlouni KM.Effects of short term metformin administration on androgens in diabetic men.Saudi med J 2004;25:75-8
10. shegem NS, Nasir AM ,Jbour AK, Batieha AM.EL –Shanti H ,Ajlouni KM. Effects of

short term metformin administration on androgens in normal men.Saudi med J 2002;23:934-7

11. Metformin improves semen characteristics of oligo-terato asthenozoospermic men with metabolic syndrome Fertil Steril 2011;95:2150–2.2011 by American Society for Reproductive Medicine.
12. Bhasin S, Cunnighham, G.R, Hayes FG et al, JCEM 95:2536-2559
13. Burke JP, Hale DE,Hazuda HP, et al. A quantitative scale of acanthosis nigricans. Diabetes care .1999;22(10):1655-9
14. Rosen Cappeleri JC ,Smith MD,et al .Development and evaluation of an abridged,5-item version of the International Index of Erectile Dysfunction(IIEF-5) as a diagnostic tool for Erectile Dysfunction.Int J Impot Res.1999 Dec:11(6):319-26
15. livingstone C, Collison M,Sex steroids and insulin resistance. Clin Sci(lond)20-02;102:151-66
16. Lin T ,Haskell J ,Vinson N,Terracio I,. Charecterisation of insulin and insulin like growth factor 1 receptos of purified leydig cells and their role in steroidogenesis in primary culture : a comparative study. Endocrinology 1986:119:1641-7
17. Bebakar WM,Honour JW,Foster D,Liu YL,Jacobs HS. Regulation of testicular function by insulin and transforming growth factor beta.Steroids1990.55,266-70
18. Pitteloud N,Hardin M,Dwyer AA,Valassi E,,Yialamas M,Elahi et al. Increase insulin resistance is associated with a decrease in leydig cell testosterone secretion in men. J Clin Endocrinol Metab 2005:90:2636-41
19. Scarpello JH,Howlett HC. Metformin therapy and clinical uses.Diab Vasc Dis Res2008 :5;157-67
20. Goodarzi MO ,Bryer Aish M. Metformin revisited :reevaluation of its properties and role in pharmacopoeia of modern antidiabetic agents. Diabetes Obes Metab 2005:7;654-65
21. Ding, E.L., Song, Y., Malik, V.S. et al. (2006) Sex differences ofendogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA, 295, 1288–1299.
22. Ding, E.L., Song, Y., Manson, J.E. et al. (2009) Sex hormone binding globulin and risk of type 2 diabetes in women and men. New England Journal of Medicine, 361, 1152–1163.
23. Perry, J.R., Weedon, M.N., Langenberg, C. et al. (2010) Genetic evidence that raised sex hormone binding globulin (SHBG) levels reduce the risk of type 2 diabetes. Human Molecular Genetics, 19, 535–544.
24. Casulari LA,et al. Minerva Endocrinol. 2010 Effects of metformin and short term lifestyle modification on the improvement of male hypogonadism associated with metabolic syndrome
25. Chen Hsun Ho, Hong Jeng Yu, Chih Yuan Wang, Fu Shan Jaw, Ju Ton Hsieh, Wan Chung Liao, Yeong Shiau Pu, Shih Ping Liu Prediabetes Is Associated with an Increased Risk of Testosterone Deficiency, Independent of Obesity and Metabolic Syndrome
26. Contreras C, Sanchez A, Martinez P, et al. Insulin resistance in penile arteries from a rat model of metabolic syndrome. Br J Pharmacol 2010;161:350-64.
27. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173-94.
28. Durand MJ, Gutterman DD. Diversity in mechanisms of endothelium-dependent vasodilation in health and disease. Microcirculation 2013;20:239-47.

29. Kim YW, Park SY, Kim JY, et al. Metformin restores the penile expression of nitric oxide synthase in high-fat-fed obese rats. J Androl 2007;28:555-60.
30. Vitale C, Mercuro G, Cornoldi A, et al. Metformin improves endothelial function in patients with metabolic syndrome. J Intern Med 2005;258:250-6.
31. Knoblovits P, et al "Metformin improves erectile function in nondiabetic patients with insulin resistance and erectile dysfunction" J Clin Endocrinol Metab 2009; 94(6 suppl): Abstract P2-347.
32. Metformin Improves Vascular Function in Insulin-Resistant Rats Prasad V.G. Katakam, Michael R. Ujhelyi, Margarethe Hoenig, Allison W. Miller