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Effect of intensive lifestyle modification & metformin on cardiovascular risk in prediabetes: A pilot randomized control trial

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***Background & objectives*: Prediabetes is associated with increased prevalence of cardiovascular disease (CVD). In participants with prediabetes, the effects of exercise and metformin were evaluated on high-sensitivity C-reactive protein (hsCRP) and carotid intima-media thickness (CIMT), surrogate markers of atherosclerosis and CVD compared with standard care.**

***Methods*: In a pilot randomized control trial, the participants were randomized in to three arms: standard care (STD), intensive lifestyle modification (ILSM) or ILSM and metformin (ILSM+Met) and followed up for six months. Monitoring of ILSM was done by a trained healthcare facilitator. hsCRP, CIMT and other relevant parameters were measured before and after intervention.**

***Results*: A total of 103 participants were randomized into three arms and followed up for six months. At six months, there was a reduction from baseline in weight and fasting blood sugar (FBS) ($P<0.01$) in all three arms and a reduction in haemoglobin A_{1c} ($P=0.03$) only in the ILSM+Met arm. The differences in hsCRP over six months within the STD, ILSM and ILSM+Met arms were −0.12 (95% confidence interval, −1.81, 2.08), −0.58 (−2.64, 0.43) and −0.11 (−1.84, 1.56), respectively. There was no difference in hsCRP, CIMT (right) or CIMT (left) between the three arms at six months.**

***Interpretation & conclusions*: There was a reduction in weight and FBS from baseline in all three arms. There was, however, no difference seen in hsCRP and CIMT in the two intervention arms compared to standard care. Larger studies with long-term follow up need to be done to detect differences in risk markers for CVD in prediabetes.**

Key words Carotid intima-media thickness - healthcare facilitator - high-sensitivity C-reactive protein - lifestyle modification - metformin - prediabetes

One of the leading risk factors and causes for disability-adjusted life years in India in 2016 was high fasting plasma glucose (FPG) and ischaemic heart disease, respectively. The disease and risk factor burden compels the need for specific health planning and primary prevention strategies[1]. Elevated levels of cardiovascular disease (CVD) risk factors and increased prevalence of CVD are seen in individuals with prediabetes[2,3]. The Indian Diabetes Prevention Programme study showed a relative risk reduction of

nearly 30 per cent for the development of diabetes with lifestyle modification (LSM) and metformin[4]. A study in the United States revealed that half of the decline in CVD death was due to improvements in risk factors; 79 per cent attributable to primary prevention and 21 per cent to secondary prevention[5]. Chronic subclinical inflammation is associated with the prediabetic state. A significant linear increase in the incidence of diabetes is seen with increasing quartiles of high-sensitivity C-reactive protein (hsCRP)[6]. hsCRP level decreases with interventions such as LSM and drugs such as statins and metformin[7]. Studies among those with prediabetes have shown reduction in the hsCRP levels by 30-40 per cent over one year through LSM and metformin[8,9].

Carotid intima-media thickness (CIMT) is a close marker of early atherosclerosis and is a widely accepted surrogate end-point for cardiovascular events[10,11]. CIMT levels are elevated in population with prediabetes as compared to controls[12,13]. Elevated hsCRP and CIMT levels are associated with cardiovascular risk factors and assess the risk of cardiovascular events[12,14]. There are very few studies on hsCRP and CIMT in prediabetes from India. Therefore, this study was conducted to evaluate the effects of intensive LSM and metformin on hsCRP and CIMT, surrogate markers of CVD to assess the risk of future cardiovascular events among participants with prediabetes.

Material & Methods

A pilot, three arm and open labelled, randomized control trial was conducted on participants with prediabetes. The study was approved by the Institutional Ethics Committee of St. John's Medical College Hospital, Bengaluru, India. Written informed consent was obtained from all participants. The study was registered at the Clinical Trials Registry of India (CTRI/2012/10/004083).

All individuals (non-diabetic adults visiting for general health check-ups or non-serious illness) tested for fasting blood sugar (FBS) or random blood sugar and confirmed prediabetes status, from medicine and endocrinology out-patient departments of St. John's Medical College Hospital, were screened from 2012 to 2014. Prediabetes was determined according to the American Diabetes Association (ADA) 2011 guidelines[15]. Study participants included adults (≥18 yr), fulfilling the criteria for prediabetes (FPG 100-125 mg/dl: IFG or 2 h plasma glucose in the 75 g oral glucose tolerance test (OGTT 140-199 mg/dl: IGT or A_{1c} 5.7-6.4%), who were free of CVD and consented to participate in the study. Participants with any contraindications to metformin (*e.g.,* respiratory disease, heart failure, renal, hepatic disease and glucocorticoid therapy) were excluded. The participants were randomized into three arms using a central computer-generated random number sequence (SPSS, PASW statistics for windows, version 18, Chicago: SPSS Inc.) in a 1:1:1 allocation ratio. Interventions were provided at baseline, three and six months after randomization (Figure).

The healthcare facilitator (HCF) was trained over two weeks to gain working knowledge of diabetes and CVD, to measure blood pressure, body mass index (BMI) and the waist-hip ratio (WHR), respond to queries and report clinical status to investigators.

Interventions: The interventions (intensive LSM and metformin adherence) were reinforced by the HCF through weekly reminders sent *via* standardized short message service and phone calls made every month. Participants randomized to standard (STD) arm received advice on standard lifestyle modification measures through moderate intensity activity[15] and dietary changes (prediabetes diet chart) by a qualified nutritionist. Participants randomized to intensive lifestyle modification (ILSM) arm received advice on standard LSM, but implementation was made intensive by adherence monitoring by the HCF. Participants randomized to ILSM+metformin (ILSM+Met) arm received intensive LSM+metformin 500 mg twice daily. At baseline, clinical history, current medication use and risk factors for CVD were recorded. Participants randomized to ILSM and ILSM+Met arms were also provided with a diary to record adherence. At three and six months visits, participant's diaries were checked and empty blister packs for metformin were obtained to verify adherence.

At baseline, three and six months, all participants had BMI, waist circumference (WC) and WHR measured. BMI was calculated as weight in kg divided by the square of height in metres (kg/m^2). WC was obtained at the midpoint between the anterior superior iliac crest and the lowest rib. Hip circumference was measured at the level of the maximal gluteal protrusion. WHR was calculated as waist circumference (cm) divided by hip circumference (cm)[16]. FBS, haemoglobin A_{1c} (HbA_{1c}), lipid profile, hsCRP and bilateral CIMT were measured at baseline and at the end of the study. Self-investigated OGTT reports of participants were included for the study.

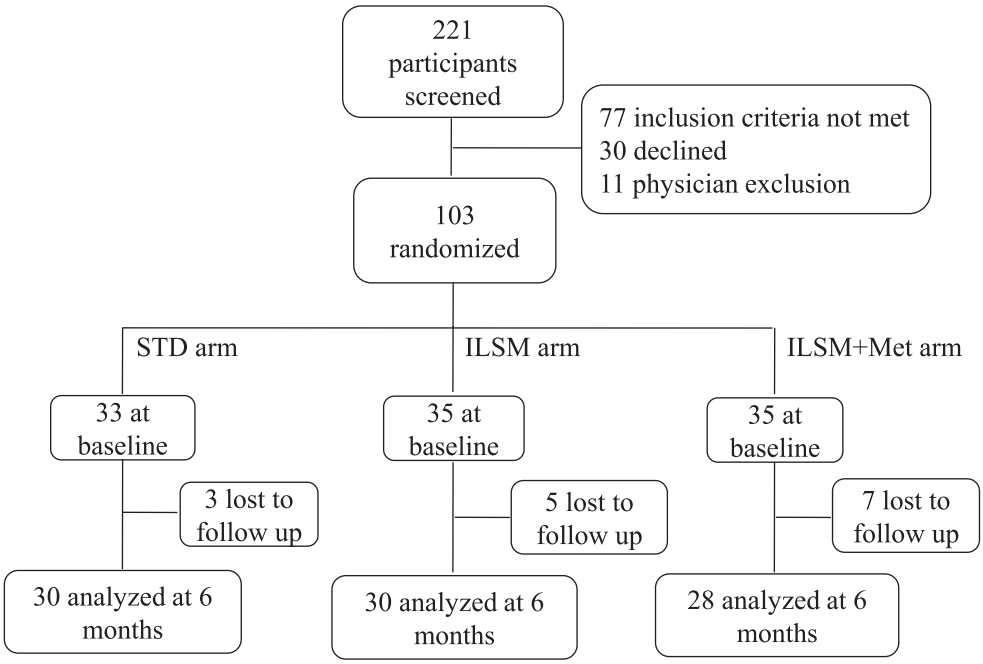

Figure. Study flowchart showing inclusion of patients. STD, standard; ILSM, intensive lifestyle modification; ILSM+Met, intensive lifestyle modification and metformin.

Measurement of CIMT & hsCRP: A qualified radiologist, blinded to the arm allocation of participants used a high-resolution B-mode carotid artery ultrasound [General Electric (GE), voluson 730 Pro, GE medical systems, Kretz ultrasound, Austria] with linear probe (9-11 MHz) to measure intima-media thickness of the posterior walls of bilateral common carotid arteries at two different predetermined sites. Maximum CIMT was calculated, and the averages of two readings were taken for each side.

hsCRP was measured using an immunoturbidimetric assay with normal levels at 0-1 mg/dl. Blood was collected in 3 ml syringes, transferred to vacutainers and serum separated at 894 g using REMI PR 23 centrifuge and aliquoted to cryotubes for storage at −80°C. Blood samples were analyzed in the central laboratory using Siemens, for USA, Cardiophase high sensitivity CRP flex reagent cartridge and CCRP calibrator, Siemens Healthcare Diagnostics Inc., Newark, USA.

Metformin: Metformin (500 mg) tablets were provided from a single batch (USV Pharmaceutical Limited, Mumbai, India). The tablets were re-packaged in similar packs with appropriate labelling and instructions.

Statistical analysis: Statistical analysis was performed using (SPSS, PASW statistics for windows, version 18, Chicago: SPSS Inc.). Analysis was done as per intention to treat protocol. Descriptive statistics such as frequencies, mean and standard deviation were calculated. Normality of distribution was assessed using Kolmogorov-Smirnov test. Student's paired *t* test was used to compare the difference in means before and after the intervention in each arm for normally distributed data. Categorical variables were compared using Chi-square and Fisher's exact test as appropriate. Changes due to the intervention were compared across groups by repeated-measures ANOVA. Correlation between variables was assessed using Pearson's correlation coefficient/Spearman's rho as appropriate.

Results

In all, 103 participants with prediabetes were screened and 85 per cent participants had complete data at six months (Figure). Of the 103 participants, 33 were randomized to STD arm, 35 to ILSM and 35 participants to ILSM+Met arms, respectively. At six months, data were analyzed on 30 participants (91%) from STD, 30 (85.7%) from ILSM and 28 (80%) from ILSM+Met arms, respectively.

In the study population of 103, the mean age was 48±10 yr, with 69 females (66.9%) and 34 males (33.1%). Ninety three (90.3%) participants came from urban and 10 (9.7%) from rural backgrounds.

Table I. Baseline characteristics of subjects by treatment allocation

Variables	Overall (n=103) n (%)	STD arm (n=33) n (%)	ILSM arm (n=35) n (%)	ILSM+Met arm (n=35) n (%)
Age (mean±SD)	47.9±10.1	49.0±9.8	45.3±10.9	49.4±9.2
Sex				
Male	34 (33.1)	10 (30.3)	10 (28.6)	14 (40.0)
Female	69 (66.9)	23 (69.7)	25 (71.4)	21 (60.0)
Area of residence (rural)	10 (9.7)	4 (12.1)	3 (8.6)	3 (8.6)
Area of residence (urban)	93 (90.3)	29 (87.9)	32 (91.4)	32 (91.4)
Family history of DM	40 (38.8)	12 (36.4)	14 (40.0)	14 (40.0)
Family history of HTN	35 (33.9)	9 (27.3)	13 (37.1)	13 (37.1)
Family history of CVD	6 (5.8)	1 (3.0)	2 (5.7)	3 (8.6)

STD, standard; ILSM, intensive lifestyle modification; ILSM+Met, intensive lifestyle modification and metformin 500 mg twice daily; DM, diabetes mellitus; HTN, hypertension; CVD, cardiovascular disease; SD, standard deviation

Family histories of diabetes mellitus were recorded in 40 (38.8%), hypertension in 35 (34%) and CVD in six (5.8%). Ninety eight participants (95%) were non-smokers and ninety nine (96%) were alcohol non-consumers.

The baseline characteristics and biochemical parameters across all three arms were overall well-matched (Tables I & II). At six months, there was a significant reduction from baseline in weight of 1.5 kg (P<0.01) and FBS of 12 mg/dl (<0.001) in all three arms. ILSM+Met arm showed a significant reduction in HbA_{1c}. There was a significant reduction in WHR, LDL cholesterol and triglyceride (TG) levels in STD arm (Table II). Despite significant reductions in variables in individual arms from baseline to six months, the delta change between the three arms at the end of six months was not significant, except in WHR and triglyceride level, which was seen in the STD arm as compared to the other two arms (Table III). There was a significant correlation between BMI and hsCRP both at baseline (r=0.34) and six months (r=0.45) with P<0.05.

The reduction in hsCRP in ILSM and ILSM+Met arms compared to STD arm at six months was not significant (Table II). The difference in hsCRP (median with inter-quartile range) in STD, ILSM and ILSM+Met were −0.12 (−2.08, 1.8), −0.58 (−2.64, 0.43) and −0.11 (−1.56, 1.84), respectively. The delta hsCRP did not differ significantly across the three arms at the end of six months.

The delta change in CIMT (right and left) between the three arms after intervention at six months were not significant. The non-progression of CIMT was not significant within or between the three arms. At the end of six months, the overall mean adherence rate was 85±6.5 per cent in the intervention arms. There was no significant difference in the proportion of adherence to interventions between the two intervention arms. In addition, the association between socio-demographic variables such as age, gender, occupation, area of residence and socio-economic status with adherence revealed no significant difference between the two intervention arms.

No correlation was found between hsCRP and CIMT (right) at baseline (r=0.073, P=0.470) or six months (r=0.028, P=0.801). Similarly, there was no correlation found between hsCRP and CIMT (left) at baseline (r=0.095, P=0.348) or six months (r=0.062, P=0.573).

Discussion

A significant reduction was observed from baseline in weight and FBS in all three arms at the end of the study. Addition of metformin to ILSM significantly reduced HbA_{1c} levels. Elevated levels of hsCRP were found at baseline in all the study arms. Prediabetes, being a category of increased risk for diabetes has been shown to have elevated levels of hsCRP as compared to normal population[8,13]. In our study, ILSM arm had a lower triglyceride level at baseline compared to the other two arms despite randomization, because of two outliers. All the participants had CIMT within the normal ranges for age at baseline and end of the study. This was contrary to studies which showed elevated levels of CIMT in prediabetes[17,18]. This could be because many patients who were normoglycaemic and recently turned dysglycaemic within the previous

Table II. Changes in clinical and laboratory parameters from baseline to six months by treatment allocation

Variables	STD (n=30)	ILSM (n=30)	ILSM+Met (n=28)
Weight (kg)			
Baseline	71. 6±8.6	71.9±9.0	69.7±12.6
Six months	69.9±9.3	70.4±9.8	67.8±12.6
P	<0.01	<0.01	<0.01
BMI (kg/m^2)			
Baseline	28.5±4.2	29.3±3.8	28.1±4.9
Six months	28.1±4.4	28.7±4.1	27.3±4.8
P	<0.01	<0.01	<0.01
SBP (mmHg)			
Baseline	124±10	123±13	124±10
Six months	125±12	122±8	122±10
P	0.63	0.84	0.43
WHR			
Baseline	0.88±0.05	0.88±0.06	0.86±0.06
Six months	0.87±0.06	0.88±0.06	0.87±0.06
P	0.03	0.25	0.09
FBS (mg/dl)			
Baseline	109.3±8.1	109.4±6.3	108.9±8.2
Six months	98.1±10.8	96.6±10.9	97.2±13.8
P	<0.001	<0.001	0.003
HbA_{1c} (%)			
Baseline	6.05±0.21	6.13±0.27	6.1±0.23
Six months	6.02±0.61	6.08±0.49	5.91±0.47
P	0.79	0.51	0.03
Total cholesterol (mg/dl)			
Baseline	192.4±41.1	178.5±34.5	174.5±41.2
Six months	195.6±39.0	171.4±39.5	186.4±33.9
P	0.53	0.30	0.08
HDL-C (mg/dl)			
Baseline	38.8±12.5	36.6±9.7	38.2±14.1
Six months	39.8±11.2	37.8±10.8	39.7±12.2
P	0.49	0.19	0.46
LDL-C (mg/dl)			
Baseline	121.7±30.9	118.0±28.8	105.5±32.5
Six months	130.4±29.2	110.4±28.1	113.6±28.3
P	0.04	0.15	0.09
Triglycerides (mg/dl)			
Baseline	174.2±92.1	108.9±46.4	159.8±79.4
Six months	136.1±60.4	124.0±68.5	142.9±69.4
P	0.004	0.29	0.35
Carotid_right (cm)			
Baseline	0.06±0.01	0.06±0.01	0.06±0.01

Contd...

Variables	STD (n=30)	ILSM (n=30)	ILSM+Met (n=28)
Six months	0.06±0.01	0.06±0.009	0.06±0.008
P	0.73	0.74	0.56
Carotid_left (cm)			
Baseline	0.06±0.01	0.06±0.01	0.06±0.01
Six months	0.06±0.01	0.06±0.009	0.06±0.009
P	0.005	0.57	0.41
hsCRP (mg/dl) Median (IQR)			
Baseline	3.91 (1.25, 5.73)	5.17 (2.8, 8.3)	2.58 (1.49, 6.35)
Six months	3.5 (2.19, 6.07)	3.27 (1.41, 7.9)	3.31 (1.07, 8.4)
P	0.87	0.38	0.44

Values in mean±SD except hsCRP. hsCRP, high-sensitivity C-reactive protein; SD, standard deviation; IQR, interquartile range; ILSM, intensive lifestyle modification; Met, metformin 500 mg twice daily; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; SBP, systolic blood pressure; BMI, body mass index; WHR, waist-hip ratio; FBS, fasting blood sugar

Table III. Changes in clinical and laboratory parameters between three arms at six months

Variables	STD	ILSM	ILSM+Met	*P*
Weight (kg)	−0.80 (−3.0, 0.00)	−1.0 (−3.0, 0.0)	−2.0 (−3.75, −0.17)	0.37
BMI (kg/m^2)	−0.31 (−1.2, 0.00)	−0.42 (−1.23, 0.0)	−0.76 (−152, −0.07)	0.36
SBP (mmHg)	0 (−10.0, 10.0)	0 (−10, 10)	0 (−10, 0.0)	0.53
WHR	0 (−0.01, 0.0)	0 (−0.0006, 0.009)	0.0015 (−0.0015, 0.01)	0.03
FBS (mg/dl)	−10 (−19, −4)	−12.5 (−20.3, −8.7)	−13.5 (−23.7, −0.50)	0.78
HbA_{1c} (%)	−0.15 (−0.30, 0.17)	−0.10 (−0.20, 0.10)	−0.20 (−0.40, 0.0)	0.47
Total cholesterol (mg/dl)	7.0 (−10.5, 19.5)	−2.0 (−20.0, 10.0)	11 (−16.0, 48.0)	0.14
HDL-C (mg/dl)	1.0 (−4.0, 7.0)	−2.0 (−6.5,3.0)	2 (2.0, 5.0)	0.25
LDL-C (mg/dl)	−81 (−103, −61.5)	79 (−105.5, −62.0)	−56 (−95, −37)	0.15
Triglycerides (mg/dl)	−16 (−67.0, 7.5)	8.0 (−20.0, 50)	6 (−57.2, 40.0)	0.02
hsCRP (mg/dl)	−0.12 (−2.08, 1.8)	−0.58 (−2.64, 0.43)	−0.11 (−1.56, 1.84)	0.36
Carotid_right (cm)	0 (−0.005, 0.005)	0 (−0.01, 0.006)	0 (−0.005, 0.01)	0.58
Carotid_left (cm)	0.005 (0.0, 0.01)	0 (−0.005, 0.005)	0 (−0.005, 0.01)	0.16

Values in median (IQR). IQR, interquartile range; STD, standard; ILSM, intensive lifestyle modification; Met, metformin

year were taken into the study. CIMT was reassessed at six months, which was a short duration to analyze changes in CIMT. For monitoring treatment responses in CIMT, studies have evaluated annual reduction rates[19,20]. No follow up studies of CIMT with ILSM and/or metformin are available to compare its effect over a period of time.

In this study, interventions with ILSM alone and/or metformin for six months did not show a significant difference in hsCRP levels across the three arms. Similar outcomes were noted in other studies in which metfomin blunted the effect of exercise[21,22]. However, interventions with metformin and exercise have shown to reduce hsCRP and other inflammatory biomarkers in prediabetes and diabetes thus reducing the risk for CVD[8,23,24]. This could be achieved as the studies spanned over a year and included supervised exercise sessions.

There was a significant reduction from baseline in WHR, LDL cholesterol and TG in STD arm at the end of six months. The difference in WHR and TG between the three arms was also significant in STD arm at six months. No correlation was found between hsCRP and CIMT at baseline or at six months. Hence,

a longer follow up with adequate sample size will help re-assess the effects of these interventions for significant changes in parameters and to confirm the other findings.

Our study has some limitations. The sample size was small with a short follow up period and self-reported, unsupervised ILSM and metformin adherence. There were more female participants in our study.

In conclusion, this pilot study established the feasibility of an RCT in prediabetes and clinical implication of improved outcomes using primary prevention strategies in a hospital setting. Changes noted in our study were associated with reduction in the incidence of diabetes and some CVD prevention. As the preliminary evaluation results are encouraging, studies with larger sample size and longer follow up may establish the true effects of simple interventions such as metformin and ILSM on cardiovascular risk in prediabetes.

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***Conflicts of Interest*:** None.

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