

# Beneficial effects of strategies for primary prevention of diabetes on cardiovascular risk factors: results of the Indian Diabetes Prevention Programme

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## Abstract

**I**n subjects with impaired glucose tolerance (IGT) who participated in the Indian Diabetes Prevention Programme (IDPP), abnormalities related to body mass index, waist circumference (WC), blood pressure (BP), lipid profile and electrocardiography were analysed (at baseline and third-year follow-up) in control, lifestyle modification (LSM), metformin (MET) and LSM + MET groups.

At baseline, elevated levels of low-density lipoprotein cholesterol (LDL-C) showed the highest (78.6%) and total cholesterol (TC) showed the lowest (42%) prevalence. At follow-up, prevalence of hypertension (BP  $\geq 130/\geq 85$  mmHg) had increased significantly in all groups. Cardiovascular abnormalities were lower in intervention groups, with the lowest rates in the MET group ( $p=0.013$  vs. control); the LDL-C level decreased in intervention groups.

In this programme, Asian Indian IGT subjects were observed to have a high prevalence of cardiovascular risk factors. LSM and MET had beneficial effects on the atherogenic phenotype of lipids but had no influence on blood pressure.

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**Key words:** cardiovascular risk factors, impaired glucose tolerance, lifestyle modification, lipid abnormalities, metformin, primary prevention of diabetes.

## Introduction

Lifestyle modification (LSM) involving dietary modification and regular physical activity improves the glycaemic milieu in subjects with impaired glucose tolerance (IGT).<sup>1-5</sup> The ben-

efits are seen in association with weight reduction in the obese<sup>1-3</sup> or without significant weight changes in relatively non-obese populations.<sup>4,6</sup>

Overweight and metabolic abnormalities such as insulin resistance are common antecedents for diabetes and cardiovascular disease (CVD). LSM has been shown to reduce cardiovascular risk factors in subjects in the Diabetes Prevention Program (DPP)<sup>6</sup> and in the Finnish Diabetes Prevention Study (DPS).<sup>7</sup>

In India, prevalence of IGT is high even in young adults and they also have a high prevalence of cardiovascular risk factors.<sup>8</sup> The Indian Diabetes Prevention Programme (IDPP) was a randomised, controlled prevention study performed in Indians with persistent IGT which showed that moderate but consistent LSM or use of metformin reduces the risk of conversion to diabetes by 28% in a three-year period.<sup>5</sup> IGT is an insulin-resistant condition and is a risk factor for diabetes and CVD. Dyslipidaemia, hypertension and smoking<sup>10</sup> and abdominal obesity<sup>11</sup> are well known risk factors for CVD. This analysis was carried out to look for the prevalence of these cardiovascular risk factors in the study cohort and also to find out whether the preventive measures resulted in a collateral benefit of reducing these risk factors over three years.

## Subjects and methods

In the IDPP, 531 subjects (421 male and 110 female) aged 35–55 years were recruited.<sup>5</sup> Screening was carried out using a two-hour post-glucose capillary glucose measurement and confirmatory diagnosis was made by a standard oral glucose tolerance test (OGTT) with a 75 g glucose load. Subjects found to have IGT on two occasions (two-hour post-glucose levels of  $\geq 7.8$  to  $< 11.1$  mmol/L) according to the criteria of the World Health Organization (WHO)<sup>12</sup> were included in the programme. All eligible subjects were randomised consecutively, as follows: group 1 (control), subjects were given standard healthcare advice; group 2, advice on LSM; group 3, treatment with metformin (MET) 500 mg/day; group 4, LSM plus MET (LSM+MET). The primary outcome measure was new-onset type 2 diabetes. Over a median follow-up period of 30 months, the cumulative incidence of diabetes was 55%, 39.3%, 40.5% and 39.5%, respectively, in the four groups; the risk reduction relative to the control group was 28.5% with LSM, 26.4% with MET and 28.2% with LSM+MET.

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**Table 1. Details of anthropometric and haemodynamic variables in the study groups**

	Control	LSM	MET	LSM+MET
<b>n</b>	<b>124</b>	<b>108</b>	<b>123</b>	<b>117</b>
<b>M:W</b>	<b>94:30</b>	<b>90:18</b>	<b>102:21</b>	<b>97:20</b>
Values are mean $\pm$ SD				
<b>Age (years) at baseline</b>	45.3 $\pm$ 5.6	45.9 $\pm$ 5.9	46.0 $\pm$ 5.9	46.2 $\pm$ 5.5
<b>BMI (kg/m<sup>2</sup>)</b>				
Baseline	26.3 $\pm$ 3.7	25.7 $\pm$ 3.4	25.5 $\pm$ 3.6	25.5 $\pm$ 3.3
Follow-up	26.7 $\pm$ 3.5	25.9 $\pm$ 3.4	25.6 $\pm$ 3.6	25.7 $\pm$ 3.1
<b>Waist circumference (cm)</b>				
Baseline	89.7 $\pm$ 8.2	88.9 $\pm$ 8.6	89.1 $\pm$ 9.4	89.4 $\pm$ 7.8
Follow-up	90.7 $\pm$ 8.0	89.5 $\pm$ 8.2	90.2 $\pm$ 9.0	90.1 $\pm$ 8.2
<b>Blood pressure (mmHg)</b>				
<i>Systolic</i>				
Baseline	123.3 $\pm$ 14.9	121.2 $\pm$ 14.7	120.6 $\pm$ 11.8	122.0 $\pm$ 13.7
Follow-up	120.1 $\pm$ 12.0	120.2 $\pm$ 12.8	118.7 $\pm$ 11.6	118.4 $\pm$ 12.1
				p=0.03
<i>Diastolic</i>				
Baseline	75.6 $\pm$ 8.3	74.6 $\pm$ 8.4	74.3 $\pm$ 9.1	74.7 $\pm$ 8.1
Follow-up	81.8 $\pm$ 9.6	81.6 $\pm$ 9.2	80.5 $\pm$ 8.7	79.7 $\pm$ 9.2
	p<0.001	p<0.001	p<0.001	p<0.001
Cardiovascular abnormalities (CVD events + probable CVD)	26, 19.5%	18, 14.9%	10, 7.8% *	18, 14.9%
			p=0.013	

**Key:** \* Metformin group vs. control; LSM = lifestyle modification; MET = metformin

Intergroup differences were non-significant. Intragroup variations are shown in respective columns. P values are in comparison with controls

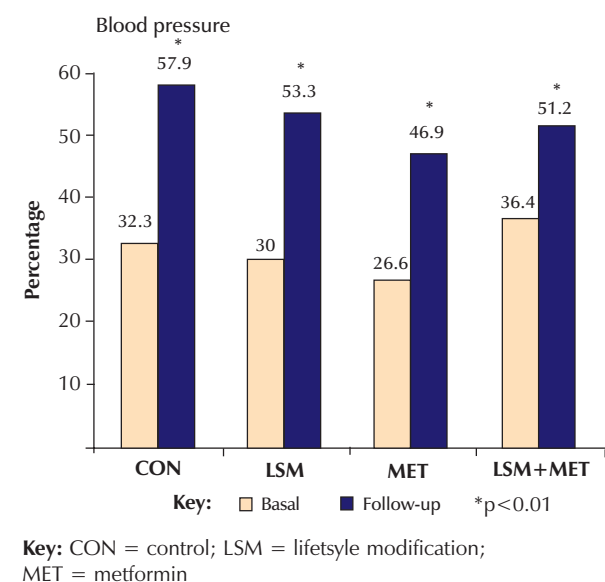
In this analysis, the changes in cardiovascular risk factors were assessed. A total of 472 subjects (383 male and 89 female) who completed a median follow-up of 30 months and for whom the required data were available were included in this analysis. The study protocol was approved by the ethics committee of the institution. Informed consent was obtained from all subjects.

Comparisons were made between baseline data and data at 30 months. Demographic details, age and gender were recorded. Height (in cm) and weight (in kg) were measured and body mass index (BMI) (kg/m<sup>2</sup>) was calculated. Waist circumference (WC) was measured. Details of blood pressure and the presence of hypertension (systolic and diastolic blood pressure  $\geq$  130/85 mmHg or receiving any anti-hypertensive agents) were recorded. Smoking  $\geq$  10 cigarettes daily was considered as current smoking.

At baseline and during annual reviews, a 12-lead ECG was recorded. Cases with major cardiac changes were excluded from recruitment. Probable CVD was diagnosed if there was a history of myocardial infarction based on treatment records, or if the trace showed pathological Q waves (Minnesota codes 1.1.1–1.2.7) or ST segment depression (codes 4.1–4.2). The ECG records were read by a cardiologist who was blinded to the study protocol; the interpretations were recorded as per the Minnesota code.

Plasma glucose (oxalate–fluoride blood) was estimated by the glucose oxidase peroxidase method. Fasting serum

**Figure 1. The prevalence of abnormalities in blood pressure at baseline and at third-year follow-up. Intragroup differences are shown**



samples were used for estimation of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and apolipoprotein B (Apo B). Low-density

**Table 2. Comparison of biochemical variables at baseline and at the final follow-up in the study groups**

	Control n=124	LSM n=108	MET n=123	LSM+MET n=117
<b>Plasma glucose (mmol/L)</b>				
<i>Fasting</i>				
Baseline	5.5±0.8	5.4±0.7	5.4±0.8	5.4±0.7
Follow-up	6.5±1.8	6.1±1.4	6.1±1.5	6.2±1.8
	p<0.001	p<0.00	p<0.001	p<0.001
<i>2 hours</i>				
Baseline	8.6±0.8	8.5±0.7	8.6±0.8	8.5±0.7
Follow-up	11.0±4.3	9.7±3.0	9.8±3.3	10.0±3.8
	p<0.001	p<0.001	p<0.001	p<0.001
<b>Total cholesterol (mmol/L)</b>				
Baseline	5.0±0.8	5.0±0.9	5.2±0.96	5.0±0.9
Follow-up	5.2±1.1	5.2±1.2	5.0±1.0	5.0±0.9
<b>Triglycerides (mmol/L)*</b>				
Baseline	1.6 (0.6–10.0)	1.7 (0.5–12.1)	1.4 (0.5–5.4)	1.6 (0.5–5.6)
Follow-up	1.7 (0.7–22.6)	1.7 (0.7–6.7)	1.5 (0.4–6.0)	1.6 (0.4–8.4)
<b>HDL-cholesterol (mmol/L)</b>				
Baseline	1.1±0.2	1.05±0.2	1.09±0.2	1.06±0.2
Follow-up	1.1±0.2	1.08±0.2	1.06±0.2	1.1±0.3
<b>LDL-cholesterol (mmol/L)</b>				
Baseline	3.1±0.8	3.2±0.8	3.4±0.9	3.2±0.8
Follow-up	3.2±0.9	2.9±0.8	3.1±0.9	2.9±0.8
		p=0.006	p=0.01	p=0.005
<b>Apolipoprotein B (mg/dL)</b>				
Baseline	104.0±23.5	107.2±19.8	104.5±22.3	105.9±21.8
Follow-up	101.3±22.7	109.8±25.1	104.3±27.2	99.6±21.6
				p=0.027
<b>TG/HDL-C</b>				
Baseline	4.4±5.1	4.5±3.1	3.9±2.4	4.1±2.5
Follow-up	4.9±4.98	4.5±3.0	4.2±2.7	4.5±3.3
<b>Key:</b> *Values are geometric mean (range). P values indicate differences between the baseline and follow-up values. Intergroup differences are not significant				

lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula. Apo B was estimated by an immunoturbidimetric method. The intra-assay coefficient of variation was < 3.6% for Apo B. All other lipid parameters were estimated using standard enzymatic procedures (Roche Diagnostics, Germany). All biochemical parameters were estimated using the Hitachi 912 auto analyzer (Roche Diagnostics, Mannheim, Germany). The technician was not aware of the identity of the samples or of the study protocol.

Cut-off values for normal lipids were: TC  $\geq$  5.2 mmol/L; TG  $\geq$  1.68 mmol/L; LDL-C  $\geq$  2.6 mmol/L; HDL-C – male < 1.0 mmol/L; female < 1.3 mmol/L; blood pressure  $\geq$  130/ $\geq$  85 mmHg; and ApoB > 98 mg/dL (0.98 mmol/L).<sup>13</sup>

#### Statistical analyses

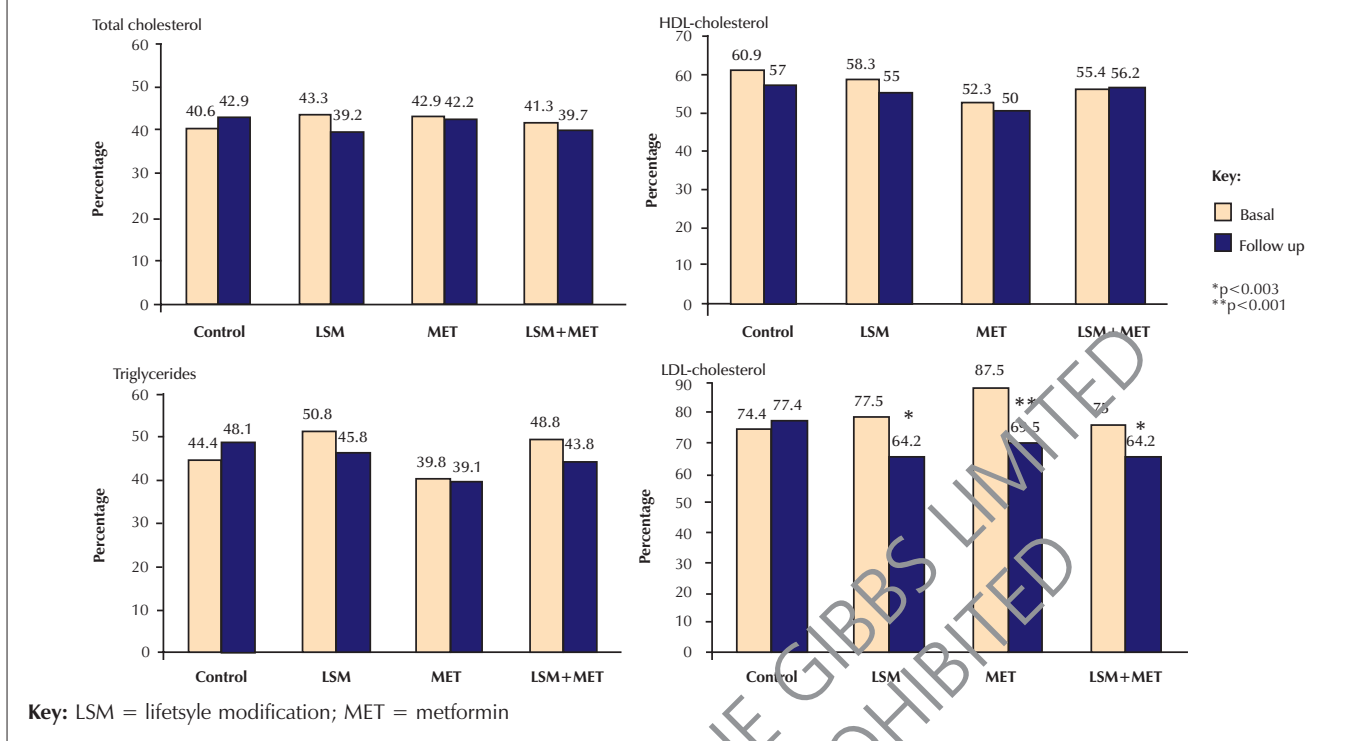
Mean and standard deviation (SD) are reported for normally distribution variables. Skewed variables were log-transformed and geometric means ( $\pm$  SD) were calculated.

Student's *t*-test, unpaired and paired, was used for intergroup and intragroup comparisons. Comparison of proportions was made using the chi-squared or 'Z' test. SPSS for Windows, version 10.0 (SPSS Inc., Chicago, IL, US) was used for analysis of data.

#### Results

The anthropometric and haemodynamic variables at baseline and at the third-year follow-up, and the development of cardiac complications at follow-up in each study group, are shown in table 1. There was no significant change in anthropometric variables in any intervention group. Systolic blood pressure decreased significantly in the LSM+MET group, but diastolic blood pressure increased significantly in all groups. Prevalence of hypertension increased in all groups, as shown in figure 1. At baseline, 32.3%, 30%, 26.6% and 36.4% of subjects had hypertension in groups 1 to 4, respectively. At follow-up, the corresponding values were 57.9%, 53.3%, 46.9% and 51.2%. The increment in the prevalence was the

**Figure 2. The prevalence of lipid abnormalities at baseline and at third-year follow-up in the study groups. Intragroup comparisons are shown**



smallest in the LSM+MET group (14.8%) ( $Z=1.98$ ,  $p=0.048$ ) vs. control (25.6%).

Adherence to dietary modifications improved from 62.5% to an average of 81.6% in the LSM group and from 62% to 81.9% in the LSM+MET group. Improvement in physical activity was from 41.7% to 58.8% in LSM while in LSM+MET it increased from 45.9% to 62.9%. The average drug adherence was 90.9% in MET and 95.1% in LSM+MET.

Smoking was reported in 61 of 420 men (14.5%) at baseline. At the third year, a total of 23 men had reduced their smoking by  $\geq 50\%$  and another nine subjects (14.8%) had stopped smoking. No statistically significant difference was seen between the control and intervention groups. The percentage who reduced their smoking was higher in intervention groups (17/37, 46%) compared to the control group (6/24, 25%); the percentage who quit smoking was similar among the two groups (16.6% in control vs. 13.5% intervention).

All the study subjects had normal ECGs at baseline. There were 11 cardiovascular events in the three-year study period (control – two; LSM – four; LSM + MET – five). A total of 61 probable CVD events were recorded on ECG between the first and third year: 24 (18%) in the control group; 14 (11.6%) in the LSM group; 10 (7.8%) in the MET group; and 13 (10.7%) in the LSM+MET group. There were three deaths which were unrelated to CVD. One death occurred during the post-operative period in a case of cerebrovascular accident in a subject in the control group. The total number of cardiovascular abnormalities at the third year was: control group 26 (19.5%); LSM group 18 (14.9%); MET group 10 (7.8%); and LSM+MET group 18 (14.9%). The difference between control and MET groups was statistically

significant for total abnormalities ( $p=0.013$ ) and for probable CVD ( $p=0.023$ ).

As expected, the mean fasting and two-hour plasma glucose values increased at follow-up as some subjects developed diabetes (table 2). There were no significant changes in the TC, TG, HDL-C or ratio of TG to HDL-C. The level of LDL-C improved significantly in all intervention groups.

At baseline, the total prevalence of lipid abnormalities was: LDL-C 78.6%; Apo B 65.9%; low HDL-C 56.7%; elevated TG 45.9%; TG/HDL-C ( $\geq 3.8$ ) 42.7%; and elevated TC 42%. In 36% of subjects, LDL-C was increased with normal levels of TC, but Apo B was abnormal in 65.9%.

Elevated TG levels were found in a larger percentage of men (48.4%) than women (36.2%) ( $\chi^2=4.48$ ,  $p=0.034$ ). Low levels of HDL-C were more common in women (84.8%) than in men (49.4%) ( $\chi^2=40.9$ ,  $p<0.0001$ ).

At follow-up, significant reductions were noted in LDL-C levels in all the intervention groups, but cholesterol and TG did not show a significant improvement (figure 2).

## Discussion

IGT is a condition associated with CVD risk factors.<sup>14-16</sup> A large proportion of the IDPP cohort had cardiometabolic abnormalities at baseline. Hypertension was present in 31.3% of subjects. Our study cohort was younger than the DPP cohort,<sup>6</sup> yet had a similar prevalence of hypertension. Dyslipidaemia also was more common in the Indians with IGT. An atherogenic phenotype with elevated levels of Apo B was present in a large proportion, which was not detected by measurement of total cholesterol. Abnormal levels of LDL-C were present in 36% of subjects who had normocholesterolaemia. It is important to note that the

atherogenic profile was seen in many subjects with IGT. Low HDL-C and elevated Apo B are important markers of atherogenicity and hence potent predictors of CVD.<sup>17,18</sup>

The percentage of subjects with abnormal LDL-C levels decreased significantly in all intervention groups during the three-year period. Improved physical activity and diet and treatment with metformin could have contributed to this finding. Metabolic syndrome as defined by the WHO criteria<sup>12</sup> was present in 41% of the IDPP cohort; at the end of three years, its prevalence was not affected by any modality of intervention.<sup>19</sup> A categorical approach to risk factors makes interpretation difficult when a number of related variables are being studied.

The DPP study demonstrated improvement in serum HDL-C and TG<sup>6</sup> and the DPS showed improvement in TG and TC/HDL-C ratio with LSM.<sup>7</sup> The DPP also found beneficial changes in the atherogenic phenotype of lipids with MET and LSM;<sup>6</sup> the benefits were greater with LSM.

In the DPP and Study to Prevent Non Insulin Dependent Diabetes Mellitus (STOP-NIDDM) trial,<sup>20</sup> beneficial effects on blood pressure were seen with LSM and acarbose, respectively. In the IDPP, new cases of hypertension were detected in all groups but the incidence of new cases over three years was significantly lower in the group treated with LSM + MET. Cardiovascular changes were lower in all types of interventions, but a statistically significant difference relative to the control group was seen with metformin treatment.

Although the study did not have the power to ascertain the effect of intervention on cardiovascular events, a reduction in electrocardiographic abnormalities, particularly with metformin, suggests that these intervention strategies might have cardiometabolic benefits.

In the STOP-NIDDM trial,<sup>20</sup> there was a 43% relative risk reduction in CVD events with acarbose treatment. The benefits were associated mainly with reduction in myocardial infarction and in incidence of hypertension. In the DPP, intensive LSM and MET treatment was associated with a reduced incidence of hypertension.<sup>6</sup>

In contrast to the DPP and DPS,<sup>6</sup> the study subjects of the IDPP were relatively non-obese, and there was no significant weight reduction or reduction in waist circumference in any group.<sup>5</sup> LSM was moderate in relation to the above studies. Therefore, the benefits in biochemical parameters were independent of weight reduction. Cessation of smoking was seen in an equal percentage of subjects in the control and intervention groups.

In summary, Asian Indian subjects with IGT were observed to have a high prevalence of cardiovascular risk factors. LSM and MET treatment had beneficial effects specifically on the atherogenic phenotype of lipids. However, it had no influence on blood pressure.

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### Conflict of interest statement

VVJ, Medical Director of U.S.V. Ltd, has contributed to the design of the study. CS, SM, AR: none declared.

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