Changes in Insulin secretion and insulin sensitivity in relation to the glycaemic outcomes in subjects with impaired glucose tolerance in the Indian Diabetes Prevention Programme -1 (IDPP-1)

Chamukuttan Snehalatha, D.Sc., Simon Mary, BSc, Sundaram Selvam, M.Phil, Cholaiyil Kizhakathil Sathish Kumar, BSc , Samith Babu Ananth Shetty, MBBS, MDRC , Arun Nanditha, MD, Ambady Ramachandran, MD

Short title: Improvement in insulin secretion and sensitivity in the IDPP-1

India Diabetes Research Foundation & Dr. A. Ramachandran’s Diabetes Hospitals
Chennai, INDIA

Address for correspondence:
Dr. A. Ramachandran, MD. Ph.D., FRCP (Lon), FRCP (Edin),
Email : ramachandran@vsnl.com

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**Objective:** Indian Diabetes Prevention Programme-1(IDPP-1), showed that life style modification(LSM) and metformin were effective for primary prevention of diabetes in subjects with impaired glucose tolerance(IGT). Among subjects followed up for 3 years (n=502), risk reduction versus control group was 28.5%, 26.4% and 28.2% in LSM, metformin and LSM+metformin groups. In this analysis, role of changes, in secretion and action of insulin in improving the outcome were studied.

**Research design and methods:** For this analysis, 437 subjects (Normoglycaemia(NGT)=93, IGT=150, Diabetes=194) were included. Measurements of anthropometry, plasma glucose and plasma insulin at baseline and at follow up were available for all of them. Indices of insulin resistance (IR,HOMA-IR) and β-cell function,(insulinogenic index (Δ I/G);(30 min-fasting insulin÷30min glucose))were also analysed in relation to the outcome.

**Results:** Subjects with IGT showed a deterioration in β-cell function with time. Persons with higher IR and/or low β-cell function at baseline had poor outcome on follow up. In relation to no abnormalities, highest incidence of diabetes occurred when both abnormalities coexisted (54.9% vs 33.7%, $\chi^2=7.53$, p=0.006). Persons having abnormal IR (41.1%) or abnormal Δ I/G (51.2%, $\chi^2=4.87$,p=0.027 vs no abnormalities) had lower incidence. Normal β-cell function with improved insulin sensitivity facilitated reversal to NGT whereas a deterioration in both resulted in diabetes. The beneficial changes were better with intervention than in the control group. Intervention groups had higher rates of NGT and lower rates of diabetes.

**Conclusions:** In the IDPP-1 subjects, beneficial outcomes occurred due to improved insulin action and sensitivity, caused by the intervention strategies.
Primary prevention studies in diabetes have been done in subjects with high risk for diabetes such as subjects with impaired glucose tolerance (IGT) (1-6) or with a history of gestational diabetes (GDM) (7). Lifestyle modification (1-5) and/or pharmacological agents like metformin (1, 5) and glitazones (6) have been shown to be effective in reducing the rate of conversion of IGT to diabetes in different ethnic groups. The benefits are seen in association with weight reduction in the obese (1, 2) or without significant weight changes in relatively non-obese population (3,5). The mechanisms that result in the beneficial changes are centered around two important pathophysiological components, namely impaired secretion and impaired action of insulin.

The Indian Diabetes Prevention Programme-1 (IDPP-1) had shown that moderate, but consistent lifestyle modification (LSM) or use of metformin (MET) reduced the risk of deterioration of IGT to diabetes by 28% in relation to a control group which had no intervention, in a three-year follow up period (5). Combining LSM with MET showed no added benefit.

IGT, an intermediate state in the natural history of type 2 diabetes is characterized by worsening in insulin resistance (IR) and insulin secretion (8). Asian Indians have higher rates of IR than Europeans and other white populations despite being relatively non-obese (9, 10).

The chief pathophysiological components of type 2 diabetes, namely impaired secretion and action of insulin are detectable many years prior to the diagnosis of clinical diabetes (11). A combined occurrence of both defects due to a gradual deterioration, eventually results in diabetes.

This analysis was done to identify the changes in insulin secretion and insulin action which produced the improved outcome with the primary prevention strategies in the IDPP-1 cohort.

RESEARCH DESIGN AND METHODS

In the IDPP-1, 531 subjects (421 male and 110 female) aged 35-55 years were recruited (5). 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 ≥ 7.8 to 11.1 mmol/L) according to the criteria of the World Health Organisation (WHO) (12) were included in the programme. All eligible subjects were randomized consecutively, as follows: group 1 (control), subjects were given standard healthcare advice; group 2, advice on LSM; group 3, treatment with MET 500 gm/day; group 4, LSM plus MET (LSM + MET). The primary outcome measure was new-onset type 2 diabetes. The measurements were done during the semi annual reviews. If a diagnosis of diabetes was made, it was confirmed by an OGTT as per the WHO criteria (12). Over a median follow-up period of 30 months, 502 subjects were available for follow up and 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. Number (%) of normoglycaemic (NGT) subjects in the four groups were 32 (24.1%), 35 (35.8%), 39 (30.5%) and 38 (31.4%), in respective order. The study protocol was approved by the ethics committee of the institution. Informed consent was obtained for all subjects.

Plasma glucose was measured using glucose-oxidase peroxidase method on Hitachi auto analyzer 912 using the reagents supplied by Roche Diagnostic Corporation, Germany. Glycosylated haemoglobin (HbA1c) was estimated by the
Improvement in insulin secretion and sensitivity in the IDPP-1 immunoturbidimetric method (Roche Reagents). Cut off value for normal was 6.0%.

Plasma insulin was measured using the Radio-Immuno Assay kit of Diasorin (Saluggia, Italy). It had a sensitivity of <24 mmol/l and the intra and inter assay coefficient of variations were less than 10%. IR was calculated using the homeostasis model assessment (HOMA-IR) (13). Insulinogenic index (Δ I/G) was calculated using the difference in the values of 30min and fasting plasma insulin (pmol/L) divided by the 30min glucose (mmol/L) (14). Cut off values for normal HOMA-IR was < 4.1 (15) and ≥ 28 for Δ I/G (16).

The relative risk reduction in the incidence of diabetes as compared with the control group was similar in the three intervention groups. Hence, the present analysis was done in control versus all intervention groups combined.

All the relevant data for this analysis were available in 437 subjects out of the 502 subjects followed up for 30 months. Comparative analyses of baseline and 3rd year data was done for NGT and IGT subjects. For the diabetic group, the baseline data was compared with the corresponding values recorded at the time of diagnosis of diabetes. The numbers of subjects with NGT, IGT and diabetes were 93, 150 and 194 respectively.

Variables included in the analysis were body mass index (BMI), waist circumference (WC), plasma glucose, plasma insulin values (0 min, 30 min and 120’min during oral GTT), HOMA-IR values and the insulinogenic index (Δ I/G). These baseline variables in the subgroup of 437 analysed were similar to that of the original cohort of 531 subjects. The differences, at the 3rd year from the baseline value were calculated. Data was computed for control and intervention groups.

Changes in plasma glucose, insulin, HOMA-IR and Δ I/G were analysed annually in the total group (control and intervention) in relation to their glucose tolerance status. Annual HOMA-IR and Δ I/G were compared with the respective baseline values for each intervention group also.

Statistical analysis: Mean and standard deviation of the variables were calculated for normally distributed variables. Inter and intra group variations were tested using paired or unpaired ‘t’ test as relevant. Data for plasma insulin, HOMA-IR and Δ I/G had skewed distribution and hence median values are shown. Inter and intra group comparisons were done using Mann-Whitney U test and Wilcoxon signed rank test respectively. Chi-square test was done to compare intergroup results. Cox’s regression analyses were done to identify the variables predictive of conversion to diabetes or to normoglycaemia. For diabetes, baseline and the corresponding values recorded at the time of diagnosis were used for analysis. For NGT and IGT, baseline and 3rd year values were analysed. Cox’s regression analyses showed that the outcome measures were influenced in the control and intervention groups by similar baseline and follow up variables. However, in the control group a few variables showed weaker association which failed to reach statistical significance (p=0.078 for HOMA-IR). This was most probably due to the smaller sample size in this group. Hence, considering the uniformity of results, the final regression analysis was done in the total sample, combining control and intervention groups. Control group was included as an independent variable. Statistical package SPSS for Windows (Version 10.0) was used (SPSS, Chicago, IL). A p value of < 0.05 was considered as significant.

RESULTS
For this analysis, 437 subjects were included. At the end of the study at 3rd year, cases with NGT, IGT and diabetes were 93, 150 and 194 respectively.

Table 1 shows the comparative data at baseline and at 3rd year review in control (n=116) versus the intervention groups (n=321). The baseline values of anthropometry and biochemical variables were similar in both groups except for a higher plasma insulin at 120min in the control group (p = 0.021). At the review, BMI was higher in the control Vs the intervention group (p=0.036). Plasma glucose increased significantly in both groups in the 3rd year. As expected, the increase was more significant in the control group. At the 3rd year, total HbA1c value increased in the control (not significant) while it showed a significant (p = 0.016) reduction in the intervention group. Significant decrease in plasma insulin values was seen in both groups. While the median HOMA-IR values showed no significant changes, the Δ I/G decreased significantly in both groups.

Outcomes of glucose tolerance at 3rd year were analysed in relation to the biochemical abnormalities categorized based on the baseline values of HOMA-IR (abnormal ≥ 4.1) and Δ I/G (abnormal < 28) (Table 2). Prevalence of diabetes was the highest in group 4 with both abnormalities (54.9%, $\chi^2$=7.53, p = 0.006 vs normal group (group 1) followed by group 3 with beta cell defect (51.2%, $\chi^2$=4.87, p = 0.027 vs group 1). Prevalence of NGT was higher in the normal group, but the intergroup differences were not statistically significant.

Table 3 shows the baseline and follow up values of HOMA-IR and ΔI/G in the control and in the total intervention group in relation to the glucose tolerance status at the follow up. Pattern of changes in IR and ΔI/G were similar in individual intervention groups, but minor statistical variations were seen due to smaller sample sizes (data not shown). Development of diabetes occurred mostly in people who had higher values of IR and lower values of Δ I/G at the baseline. On follow up, both the functions deteriorated further. On the other hand, subjects who reverted to NGT showed improvement in insulin sensitivity and secretion of insulin remained in normal ranges.

Cox’s regression analyses adjusted for the baseline age, BMI and WC showed that lower 120 min plasma glucose (β = - 0.029, HR = 0.972, p = 0.011), lower HOMA-IR (β = - 0.167, HR = 0.846, p = 0.008) and higher ΔI/G (β = 0.016, HR = 1.016, p = 0.002) at baseline and reduction in HOMA-IR (β = - 0.152, HR = 0.859, p = 0.005) and improved ΔI/G (β = 0.015, HR = 1.015, p = 0.001) improved the glucose tolerance from IGT to NGT. For diabetes, the risk was higher in those with lower 120 min insulin values (β = - 0.006, HR = 0.994, p = 0.007), higher HOMA-IR (β = 0.172, HR = 1.187, p < 0.0001) and lower ΔI/G (β = - 0.015, HR = 0.985, p=0.003) at baseline and an increase in HOMA-IR (β = 0.118, HR = 1.126, p < 0.0001) and a reduction in ΔI/G (β = - 0.016, HR = 0.984, p = 0.001) increased the hazard for diabetes.

Figure 1 shows the changes in HOMA-IR and ΔI/G in relation to the corresponding baseline values, in subjects who had normoglycaemia, IGT and diabetes, at each annual follow up. In NGT group, IR decreased significantly at all follow up, ΔI/G showed improvement in year 1 and remained normal at other periods. Those who continued to be IGT showed no significant changes in IR. Value of ΔI/G showed a significant reduction in the 3rd year. Subjects with diabetes showed increased IR and decreased ΔI/G at all time periods.

**DISCUSSION**

Significant reduction in incident diabetes with interventions in the IDPP-1
were due to improvement in β-cell function and in insulin sensitivity. Diabetes developed when IR and β-cell function deteriorated. Reversal to NGT occurred when insulin sensitivity improved and β-cell function remained normal. In the intervention group (total or each) higher proportion of subjects reverted to NGT and smaller proportion developed diabetes when compared with the control group.

Although the biochemical mechanisms causing diabetes and reversal to NGT were similar in the control and intervention groups, the benefits seen with inventions were due to augmented beneficial changes in insulin sensitivity and insulin secretion. Subjects with impaired fasting glucose (IFG) or IGT have impaired ΔI/G secretion, which may explain their high risk for conversion to diabetes (17).

In subjects with IGT, a time-related deterioration in the ΔI/G was noted. Normal β-cell function with an improved sensitivity of insulin had favoured reversal to NGT whereas a deterioration in both the functions resulted in diabetes. Persons with higher IR and/or lower β-cell capacity at the baseline had a predisposition to the adverse outcome. These findings seen in the univariate and multivariate analyses agree with the sequence of changes described by Festa et al (18) in the development of diabetes from NGT to diabetes in a longitudinal study. The Diabetes Prevention Programme (DPP) also demonstrated that the better preventive effect of intensive lifestyle was due to improved insulin sensitivity concomitant with preservation of β-cell function (19). Treatment with metformin also demonstrated similar changes, though to a lesser degree than with intensive lifestyle changes. The Finnish Diabetes Prevention Study (DPS) had shown similar effects of lifestyle modification (20). In our study, a moderate, but sustained lifestyle modification and/or metformin produced similar beneficial changes. These effects were not associated with weight loss, unlike in the DPP and DPS studies (19,20). Probably, a redistribution of body fat which is shown to occur with enhanced physical activity (21) could have improved insulin sensitivity in our study subjects. At follow up, BMI increased only in the control group while the waist circumference increased in both groups. The increase was significantly less in the intervention groups.

Compromised β-cell function is detectable in prediabetic persons long before the onset of type 2 diabetes (11, 18). The importance of declining β-cell function in the transition of NGT to IGT and IGT to diabetes, has been demonstrated in a longitudinal study in Pima Indians (22). The Insulin Resistance Atherosclerosis Study has addressed the longitudinal changes in β-cell function in a period of 5.2 years, in subjects with NGT, IGT and diabetes in multiethnic population (18). The results showed that the mean insulin sensitivity measured as an index (SI) from a frequently sampled intravenous glucose tolerance test, declined in all glucose tolerance categories with time. Importantly it was demonstrated that on follow up, the glucose tolerance status was principally maintained by the change in acute insulin response. A compensatory increase in insulin secretion maintained NGT, IGT status was due to a failure to increase insulin secretion and decreased insulin secretion led to diabetes (18). The results of the DPP (19) and the Troglitazone in Prevention of Diabetes (TRIPOD study) (7) had also demonstrated the pivotal role of β-cell dysfunction in the conversion of IGT to diabetes. β-cell function is enhanced by improved insulin sensitivity and preservation of β-cell function decreases the conversion of IGT to diabetes.

Subjects with lower baseline 120 min plasma glucose were found to have a higher probability of reversal to NGT which could be explained by the absence of above pathophysiological components. A negative
Improvement in insulin secretion and sensitivity in the IDPP-1

association between baseline 120 min plasma insulin response and development of diabetes in this study was in agreement with a similar findings by Saad et al (23).

The HOMA-IR index derived from the product of fasting glucose and insulin concentrations primarily reflects hepatic insulin resistance. It has been demonstrated that there is a 70% concordance between muscle insulin resistance and liver insulin resistance in same subjects (24).

A limitation of the study is that the estimates of insulin secretion and action have been made by calculations based on the OGTT, and not by a “gold standard” test, euglycaemic clamp study. The indices are being used in epidemiological studies as the clamp studies are not feasible in large numbers.

The early phase insulin secretion calculated as the ΔI/G, correlates with the first phase insulin release measured during hyperglycaemic insulin clamp (25).

Summarizing, the IDPP-1 study showed that a decrease in insulin secretion combined with reduced insulin sensitivity resulted in diabetes and an improvement in these functions facilitated reversal to NGT in subjects with IGT. The rate of conversion to diabetes was significantly lower and reversal to NGT was higher in subjects who received interventions than in the control group. This indicated that beneficial effects of interventions work through mechanisms of preserving β-cell function and improving insulin sensitivity even in subjects not having reduction in body weight.

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REFERENCE


Table 1: Comparison of data at baseline and at 3rd year review in control vs intervention groups

<table>
<thead>
<tr>
<th></th>
<th>Control (n=116)</th>
<th>Intervention (n=321)</th>
<th>P value Intergroup</th>
<th>P value Intragroup</th>
<th>P value Intragroup</th>
</tr>
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<tbody>
<tr>
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<tr>
<td><strong>BMI (kg/m²)</strong>*</td>
<td>Basal</td>
<td>26.0 ± 3.0</td>
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<td>0.185</td>
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<tr>
<td></td>
<td>Follow up</td>
<td>26.4 ± 3.1</td>
<td></td>
<td>0.036</td>
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<td><strong>Waist (cms)</strong>*</td>
<td>Basal</td>
<td>89.3 ± 7.4</td>
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<td>Follow up</td>
<td>90.8 ± 7.6</td>
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<td>0.426</td>
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<td><strong>Glucose (mmol/l)</strong>*</td>
<td>Basal</td>
<td>5.5 ± 0.8</td>
<td></td>
<td>0.305</td>
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<td>Follow up</td>
<td>6.5 ± 1.8</td>
<td></td>
<td>0.025</td>
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<td></td>
<td>&lt; 0.0001</td>
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<tr>
<td></td>
<td>Basal</td>
<td>9.3 ± 1.7</td>
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<td>0.174</td>
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<td></td>
<td>Follow up</td>
<td>11.0 ± 2.9</td>
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<td>0.114</td>
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<td>&lt; 0.0001</td>
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<tr>
<td></td>
<td>Basal</td>
<td>8.6 ± 0.7</td>
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<td>0.198</td>
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<td>Follow up</td>
<td>10.9 ± 4.0</td>
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<td>0.009</td>
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<td></td>
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<td></td>
<td>&lt; 0.0001</td>
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<tr>
<td><strong>HbA1c (%)</strong>*</td>
<td>Basal</td>
<td>6.2 ± 0.5</td>
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<td>Follow up</td>
<td>6.4 ± 1.2</td>
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<td>0.016</td>
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<td></td>
<td>0.140</td>
<td>0.215</td>
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<tr>
<td><strong>Insulin (pmol/l)</strong>**</td>
<td>Basal</td>
<td>120</td>
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<td>0.164</td>
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<tr>
<td></td>
<td>Follow up</td>
<td>108</td>
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<td>0.361</td>
<td>0.091</td>
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<td>432</td>
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<td>363</td>
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<td>0.04</td>
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<td>&lt; 0.0001</td>
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<td></td>
<td>Basal</td>
<td>636</td>
<td></td>
<td>0.021</td>
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<td>Follow up</td>
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<td></td>
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<tr>
<td></td>
<td>Basal</td>
<td>4.8</td>
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<td>0.115</td>
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<td>Follow up</td>
<td>4.6</td>
<td></td>
<td>0.130</td>
<td>0.194</td>
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<td></td>
<td></td>
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<td>0.293</td>
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<tr>
<td>**HOMA_IR ****</td>
<td>Basal</td>
<td>36.3</td>
<td></td>
<td>0.632</td>
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<tr>
<td></td>
<td>Follow up</td>
<td>24.0</td>
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<td>0.220</td>
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<td></td>
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<td>&lt; 0.0001</td>
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</table>

*Mean values are mean ± SD - values were compared using paired or unpaired ‘t’ test
** Median values – comparisons were done using median test
Table 2: Outcome of glucose tolerance at 3\textsuperscript{rd} year in relation to the status of baseline HOMA-IR and Delta I/G

<table>
<thead>
<tr>
<th>Groups</th>
<th>Status of IR, Delta I/G</th>
<th>(1)</th>
<th>(2)</th>
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<th>(4)</th>
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<tr>
<td></td>
<td>Both Normal</td>
<td>IR abnormal</td>
<td>ΔI/G abnormal</td>
<td>Both abnormal</td>
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<tr>
<td>n</td>
<td>92</td>
<td>168</td>
<td>86</td>
<td>91</td>
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<tr>
<td>HOMA-IR*</td>
<td>3.1</td>
<td>6.1</td>
<td>2.6</td>
<td>5.7</td>
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<tr>
<td>Delta I/G*</td>
<td>45.8</td>
<td>51.2</td>
<td>15.2</td>
<td>17.3</td>
<td></td>
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<tr>
<td>Outcome at 3\textsuperscript{rd} year</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
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<tr>
<td>NGT</td>
<td>25 (27.2)</td>
<td>34 (20.2)</td>
<td>17 (19.8)</td>
<td>17 (18.6)</td>
<td></td>
</tr>
<tr>
<td>IGT</td>
<td>36 (39.1)</td>
<td>65 (38.7)</td>
<td>25 (29.1)</td>
<td>24 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>31 (33.7)</td>
<td>69 (41.1)</td>
<td>44 (51.2)\textsuperscript{a}</td>
<td>50 (54.9)\textsuperscript{b,e}</td>
<td></td>
</tr>
</tbody>
</table>

* Median values

a - χ\textsuperscript{2}=4.87, p=0.027 vs Group (1), b- χ\textsuperscript{2}=7.53, p=0.006 vs Group (1), c – χ\textsuperscript{2}=4.03,p=0.045 vs Group (2)

Table 3: Status of insulin resistance and insulinogenic index in relation to the glucose tolerance status, in the control and intervention groups. Median values are shown.

<table>
<thead>
<tr>
<th>Status of Glucose Tolerance</th>
<th>Control (n=116)</th>
<th>Intervention (n=321)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HOMA_IR</td>
<td>Delta I/G</td>
</tr>
<tr>
<td>NGT (n=93)</td>
<td>n</td>
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</tr>
<tr>
<td>Basal</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Follow up</td>
<td>4.4</td>
<td>32.6</td>
</tr>
<tr>
<td>IGT (n=150)</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Follow up</td>
<td>4.5</td>
<td>39.6</td>
</tr>
<tr>
<td>Diabetes(n=94)</td>
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<tr>
<td>Basal</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Follow up</td>
<td>5.4</td>
<td>34.7</td>
</tr>
</tbody>
</table>

Significant P values shown are for intra group comparisons of follow up Vs baseline (Wilcoxon Rank test). Inter group: diabetes comparisons (Mann Whitney U test) a = p<0.001 Vs NGT, b = p<0.001 Vs IGT
Legend for figure
Median values of HOMA-IR and Delta I/G were calculated in relation to the glycaemic status (Normal, IGT, Diabetes) at annual followup. The median values at the 1st, 2nd and 3rd year follow up in comparison with the corresponding baseline values in these participants are shown in each category of glucose tolerance. Numbers in brackets show the participants who had normoglycaemia, impaired glucose tolerance or diabetes at the respective annual follow up. * p<0.05 vs baseline values.

**Normoglycaemia**

**HOMA-IR**

- **Baseline**
  - Year 1: 4.6
  - Year 2: 4.5
  - Year 3: 4.6

- **Follow up**
  - Year 1: 4.5
  - Year 2: 4.5
  - Year 3: 4.5

**Delta I/G**

- **Baseline**
  - Year 1: 34.2
  - Year 2: 41.2
  - Year 3: 40.5

- **Follow up**
  - Year 1: 42.1
  - Year 2: 41.2
  - Year 3: 40.4

(1st year n=160, 2nd year n=155, 3rd year n=93)

**Impaired glucose tolerance**

**HOMA-IR**

- **Baseline**
  - Year 1: 4.5
  - Year 2: 4.6
  - Year 3: 4.5

- **Follow up**
  - Year 1: 4.5
  - Year 2: 4.5
  - Year 3: 4.5

**Delta I/G**

- **Baseline**
  - Year 1: 28.3
  - Year 2: 34.8
  - Year 3: 38.8

- **Follow up**
  - Year 1: 31.7
  - Year 2: 34.5
  - Year 3: 30.7

(1st year n=201, 2nd year n=152, 3rd year n=150)

**Diabetes**

**HOMA-IR**

- **Baseline**
  - Year 1: 28.9
  - Year 2: 29.5
  - Year 3: 27.3

- **Follow up**
  - Year 1: 20.1
  - Year 2: 18.4
  - Year 3: 18.5

(1st year n=70, 2nd year n=60, 3rd year n=64)