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# Normalization of glucose intolerance in first-degree relatives of patients with type 2 diabetes

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ABSTRACT

*Aims:* The aim of this study was to estimate the conversion rate to normal glucose tolerance (NGT) from a state of abnormal glucose metabolism and to identify characteristics predicting the conversion rate in first-degree relatives (FDRs) of patients with type 2 diabetes with glucose intolerance.

*Methods:* A total of 2368 (614 men and 1754 women) FDRs of consecutive patients with type 2 diabetes aged 20–70 years in 2003–2005 were followed through 2007. Glucose tolerance classification was based on the criteria of the American Diabetes Association base on standard 75 g 2-h oral glucose tolerance test. The study group consisted of 370 participants with glucose intolerance at baseline.

*Results:* The conversion rates to normal glucose tolerance from impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) were 16.2% (95% confidence interval (CI) 13.30, 19.10) and 10.9% (95% CI: 5.7, 16.1) per year after an average of 2 years, respectively. Lower baseline fasting plasma glucose (HR 1.02, 95% CI: 1.01, 1.04) and 2-h (HR 1.02, 95% CI: 1.01, 1.04) glucose predicted conversion to NGT, as did changes in body mass index (BMI), waist circumference (WC), and lipids.

*Conclusions:* This is the first estimate of conversion rate and predictors from IFG and IGT to NGT in FDRs of people with type 2 diabetes in Iran. Lower baseline fasting, 2-h plasma glucose and changes in BMI, WC, and lipids predicted reversal to NGT at 24 months follow-up.



## 1. Introduction

The progression from normal glucose tolerance (NGT) to type 2 diabetes occurs through an intermediate state of glucose intolerance known as pre-diabetes (i.e., impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)). This transition is usually a gradual phenomenon that occurs over 5–10 years [1], depending on the population studied. Individuals who are older, overweight, have higher level of blood glucose and other diabetes risk factors are more likely to progress. Moreover, low insulin secretion and severe insulin resistance identify individuals more likely to progress to diabetes [2].

Previous studies from our group and others reported a high prevalence of pre-diabetes among first-degree relatives (FDRs) of people with type 2 diabetes [3,4]. Despite the high risk of progression to diabetes from a state of glucose intolerance in FDRs of patients with diabetes, there is a paucity of prospective data on the conversion rate to NGT from glucose intolerance state in this population. Some studies have estimated progression rates and factors cause the deterioration from NGT to pre-diabetes and further to diabetes in

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general or selected populations [5–13], whereas the reverse process less often discussed [14–16]. A substantial number of individuals with IGT and/or FPG not only did not progress but, in fact, returned to NGT over time, but the proportion varies between studies range from 16.8% to 62.8% with observation period of between 6 weeks and 10 years [1,16–29]. In contrast to the vast literature about predictors of deterioration of glucose tolerance [30], far less is known about factors associated with reversal of the process [14,15].

The objective of this study therefore was to estimate the conversion rates to NGT from IFG and/or IGT and to conduct a preliminary investigation of the determinants of reversal to the NGT in FDRs of patients with type 2 diabetes.

## 2. Subjects and methods

### 2.1. Data collection

The Isfahan Diabetes Prevention Study (IDPS) is an ongoing cohort study in central Iran to assess the efficacy of intensive diet and exercise to prevent or delay the onset of type 2 diabetes mellitus in FDRs of patients with type 2 diabetes. The study was established in 2003–2005 when 2368 (614 men and 1754 women) FDRs of a consecutive sample of patients with type 2 diabetes attending clinics in Isfahan Endocrine and Metabolism Research Center which is affiliated to Isfahan University of Medical Sciences, Iran, completed laboratory tests including standard 75 g 2-h oral glucose tolerance test (OGTT) and a questionnaire on their health status and on various potential risk factors for diabetes. Participants receive follow-up tests according to Standard of Medical Care in Diabetes [31] to update information on demographic, anthropometric, and lifestyle factors and on newly diagnosed diabetes, IGT and IFG. Accordingly, if OGTT was normal at baseline, repeat testing was carried out at least at 3-year interval. Otherwise, repeat testing was carried out annually. The IDPS baseline methods have been described in detail elsewhere [32]. The participants included siblings and children of patients with type 2 diabetes. All participants were referred for nutritional and weight management program after the start of the study by qualified nutritionists to give detailed information and education about diabetes risk factors and prevention and if necessary recommend weight management program. Subjects with diabetes at baseline and follow-ups were referred to primary care, and all other subjects with abnormal glucose metabolism were informed about the result and that lifestyle changes could be beneficial.

### 2.2. Ascertainment of glucose intolerance

Cases of IGT, IFG and diabetes were identified from baseline and follow-up OGTTs according to American Diabetes Association criteria [33]. Individuals who were not diabetic at baseline but had IFG or IGT and who had at least one subsequent examination were included. Pregnant women were excluded. For the present study, analyses were limited to the 370 participants (71 men and 299 women, mean (SD) age 43.4 (6.7) years) in the average 24 months follow-up for whom complete data were available.

### 2.3. Procedures

Information on age, gender, body size, glycosylated hemoglobin ($HbA_{1c}$), cholesterol, LDL HDL, triglyceride and blood pressure (BP), family and personal medical history was collected at the baseline and through follow-ups. The same methodology was used at baseline and follow-ups. Participants reported to clinics in the morning after an overnight fast. Subjects were asked to abstain from vigorous exercise in the evening before and in the morning of the investigations. Smokers were encouraged to abstain from smoking in the morning of the investigations. First on arrival at the clinic, the information given by the participants in the questionnaire on family history was verified. Then, with the subjects in light clothes and without shoes height, weight, waist and hip circumference were measured using standard apparatus. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height, waist, and hip circumference were measured to the nearest 0.5 cm with a measuring tape. Waist was measured midway between the lower rib margin and the iliac-crest at the end of a gentle expiration. Hip circumference was measured over the greater trochanters directly over the underwear. Resting BP was measured after subjects had been seated for 10 min by using a mercury sphygmomanometer and appropriately sized cuffs, using standard techniques. Fasting plasma glucose (FPG) was measured using the glucose oxidase method. Subjects with FPG $<$ 126 mg/dl underwent a standard OGTT (75 g glucose 2-h) at baseline and the follow-ups. Venous blood was sampled at fasting, 30, 60, and 120 min after oral glucose administration. Plasma samples obtained after centrifuge were analyzed on the same day.

$HbA_{1c}$ (measured by ion-exchange chromatography), total cholesterol, triglyceride, HDL, and LDL (calculated by the Friedewald equation [34]) were also assessed. All the blood sampling procedures were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Center using enzyme-linked method. Tenets of the Declaration of Helsinki were followed, Institutional Ethical Committee approval was granted, and an informed consent form was signed by each participant.

### 2.4. Definitions

We calculated body mass index (BMI) as the ratio of weight (kg) to height squared ($m^2$), the latter being assessed at baseline only. Diabetes was defined if: (i) two times FPG $\geq$ 126 or (ii) one time 2-h plasma glucose of $\geq$200 mg/dl or (iii) self-report of diabetic treatment. IGT was defined as FPG $<$ 126 mg/dl, but with 2-h PG concentration $\geq$140 and $<$200 mg/dl. If FPG was in the range of 100–126 mg/dl and 2-h PG was $<$140 mg/dl, it was considered as IFG. If the FPG was below 100 mg/dl and 2-h PG smaller than 140 mg/dl, it was considered a sign of NGT (30).

The National Cholesterol Education Program Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III (NCEP-ATP III)) [35] definition was used for the metabolic syndrome (MetS) by the presence of 3 or more of the 5 abnormalities: (i) BP $\geq$130/85 mmHg or a history of hypertension and current use of antihypertensive treatment; (ii) waist girth $>$102 cm for men

**Table 1 – Age-adjusted means (SE) of selected characteristics among 71 men and 299 women.**

| Characteristics | Age-adjusted mean (SE) | | Difference (95% CI) |
|---|---|---|---|
| | Men ($n$ = 71) | Women ($n$ = 299) | |
| Age (yr.) | 43.3 (0.8) | 43.5 (0.4) | −0.2 (−1.95, 1.55) |
| Height (cm) | 168.5 (0.7) | 155.9 (0.3) | 12.6 (11.2, 14.2)*** |
| Weight (kg) | 79.6 (1.3) | 73.1 (0.6) | 6.5 (3.84, 9.36)*** |
| Body mass index (kg/m$^2$) | 28.0 (0.5) | 30.1 (0.2) | −2.1 (−3.13, −1.07)*** |
| Waist circumference (cm) | 95.8 (1.0) | 89.0 (0.5) | 6.8 (4.62, 8.98)*** |
| Hip circumference (cm) | 105.4 (1.1) | 109.8 (0.5) | −4.4 (−6.83, −2.00)*** |
| Fasting glucose baseline (mg/dl) | 101.8 (1.4) | 101.9 (0.7) | −0.1 (−3.07, 2.87) |
| Plasma glucose 30 min (mg/dl) | 170.2 (3.7) | 159.6 (1.8) | 10.6 (2.57, 18.6)*** |
| plasma glucose 60 min (mg/dl) | 187.9 (4.6) | 178.5 (2.3) | 9.4 (−0.73, 19.5) |
| Plasma glucose 120 min (mg/dl) | 149.8 (3.1) | 154.1 (1.52) | −4.3 (−11.10, 2.53) |
| $HbA_{1c}$ (%) | 5.1 (0.1) | 5.1 (0.06) | 0.0 (−0.27, 0.27) |
| Cholesterol (mg/dl) | 203.8 (5.1) | 201.4 (2.5) | 2.4 (−32.8, 36.40) |
| LDL-cholesterol (mg/dl) | 122.2 (4.4) | 119.3 (2.1) | 2.9 (−6.95, 12.4) |
| HDL-cholesterol (mg/dl) | 42.9 (1.5) | 47.3 (0.7) | −4.4 (−7.66, −1.14)** |
| Triglyceride (mg/dl) | 206.2 (13.5) | 175.1 (6.6) | 31.1 (0.56, 59.6)* |
| Systolic BP (mmHg) | 118.6 (2.0) | 115.5 (0.1) | 3.1 (−1.39, 7.59) |
| Diastolic BP (mmHg) | 76.6 (1.6) | 74.5 (0.08) | 2.1 (−1.45, 5.65) |
| Obesity, no. (%) | 17 (24.3) | 140 (47.1) | −22.9 (−34.40, −11.30)** |
| Impaired fasting glucose, no. (%) | 13 (18.3) | 42 (14.0) | 4.3 (−5.5, 14.1) |
| Impaired glucose tolerance, no. (%) | 58 (81.7) | 257 (86.0) | −4.3 (−14.1, 5.5) |
| Reverted from IFG to NGT, no. (%) | 3 (23.1) | 12 (28.6) | −5.5 (−32.20, 21.20) |
| Reverted from IGT to NGT, no. (%) | 19 (32.8) | 80 (31.1) | 1.6 (−11.7, 15.00) |

Age-adjusted means were calculated using general linear models. Data are expressed as mean (SE) or number (%). The difference in the mean or percentage of the variables between men and women. CI = confidence interval.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$

and >88 cm for women, (iii) serum triglyceride ≥150 mg/dl (1.7 mmol/L) and/or (iv) HDL-cholesterol (<40 mg/dl (0.9 mmol/L) for men and <50 mg/dl (1.0 mmol/L) for women), and (v) FPG levels ≥110 mg/dl (6.1 mmol/L).

### 2.5. *Determination of reverting to NGT over time*

Conversion rates were estimated as the number of conversion to NGT cases from pre-diabetes per 100 person-years of follow-up. As the relevant period was considered the date of completion of the baseline examination between 2003 and 2005 until the either (i) occurrence of NGT, (ii) the date of the last completed follow-up, (iii) death, or (iv) end of follow-up on December 31, 2007, whichever came first. For ease of interpretability, we report the conversion rates in terms of percent per year.

### 2.6. *Statistical analysis*

Statistical methods used included the Student's *t*-test, chi-squared test, and Cox's proportional hazards model. Age-adjusted means were calculated and compared using general linear models. Analysis was performed using software SPSS version 11.0 for windows© (SPSS Inc., Chicago, IL). Analyses were initially stratified by gender, but as the findings were similar, the results are presented for both gender combined to increase statistical power. All tests for statistical significance were two-tailed, and performed assuming a type I error probability of <0.05.

## 3. Results

### 3.1. *Characteristics*

The baseline characteristics of the 71 men and 299 women with glucose intolerance are shown in Table 1. Women had lower height and weight, triglyceride and 30 min PG, than men. Men had lower BMI, waist circumference (WC), hip circumference (HC), HDL and proportion of obesity than women. The mean (SD) age of men was 43.3 (6.4) years and 43.5 (6.8) years for women. Men and women had similar $HbA_{1c}$ levels. 10.0% of the men and 10.4% of women had desirable weights. Overall, 90.0% men and 89.6% women were overweight or obese (BMI ≥ 25), and 24.3% men and 47.1% women were obese (BMI ≥ 30). 32.8% of men and 31.1% of the women reverted from IGT to NGT, with no significant difference between genders. There were no significant gender differences in frequency of reverting from IFG to NGT (23.1% in men vs. 28.6% in women).

The baseline characteristics of the 315 (85.1%) participants with IGT and 55 (14.9%) with IFG are shown in Table 2. At baseline, age, height, WC, HC, BMI, cholesterol, LDL, HDL triglyceride, BP and proportion of obesity and MetS were similar for individuals with IGT and IFG. Participants with IGT had higher age-adjusted mean PG at 60 and 120 min. The IFG group had higher fasting PG, weight and $HbA_{1c}$. The mean (SD) age was 43.5 (6.7) years for those with IGT and 42.9 (6.6.) years for those with IFG. MetS was present in over a quarter of the participants.

**Table 2 – Age, age-adjusted mean (SE) and proportion characteristics[†] of first-degree relatives of patients with type 2 diabetes by glucose intolerance status at baseline, the Isfahan Diabetes Prevention Study.**

| Baseline characteristic | IGT ($n$ = 315) | IFG ($n$ = 55) | Difference (95% CI) |
|---|---|---|---|
| Age (year) | 43.5 (0.4) | 42.9 (0.9) | 0.6 (−1.32, 2.52) |
| Height (cm) | 158.1 (0.4) | 159.7 (1.0) | −1.5 (−3.69, 0.69) |
| Weight (kg) | 73.8 (0.6) | 77.6 (1.5) | −3.8 (−7.02, −0.78)* |
| Waist circumference (cm) | 90.1 (0.5) | 91.0 (1.2) | −0.9 (−3.41, 1.61) |
| Hip circumference (cm) | 108.6 (0.5) | 111.0 (1.2) | −2.4 (−5.05, 0.25) |
| Body mass index (kg/m$^2$) | 29.5 (0.2) | 30.5 (0.5) | −1.0 (−2.15, 0.15) |
| Fasting glucose baseline (mg/dl) | 101.0 (0.6) | 106.8 (1.5) | −5.8 (−8.94, −2.46)*** |
| Plasma glucose 30 min (mg/dl) | 161.1 (1.8) | 164.7 (4.2) | −3.9 (−12.19, 5.33) |
| Plasma glucose 60 min (mg/dl) | 184.4 (2.1) | 156.9 (5.1) | 27.2 (17.10, 38.50)*** |
| Plasma glucose 120 min (mg/dl) | 161.3 (1.0) | 106.7 (2.4) | 51.4 (49.60, 59.80)*** |
| $HbA_{1c}$ (%) | 5.1 (0.05) | 5.4 (0.1) | −0.2 (−0.58, −0.01)* |
| Cholesterol (mg/dl) | 200.7 (2.4) | 208.7 (5.8) | −7.9 (−18.9, 5.28) |
| LDL-cholesterol (mg/dl) | 119.6 (2.0) | 123.8 (5.1) | −4.7 (−14.9, 7.18) |
| HDL-cholesterol (mg/dl) | 46.1 (0.7) | 49.1 (1.8) | −3.1 (−6.73, 0.73) |
| Triglyceride (mg/dl) | 182.2 (6.4) | 174.4 (15.6) | 8.4 (−12.00, 30.00) |
| Systolic BP (mmHg) | 115.8 (0.9) | 117.8 (2.4) | −2.0 (−7.01, 3.21) |
| Diastolic BP (mmHg) | 74.7 (0.8) | 76.4 (1.9) | −1.8 (−5.83, 2.23) |
| Men, no. (%) | 58 (18.4) | 13 (23.6) | −5.2 (−17.20, 6.79) |
| Obesity (BMI $\geq$ 30), no. (%) | 128 (40.9) | 29 (53.7) | −12.1 (−26.4, 2.17) |
| Metabolic syndrome, no. (%) | 90 (28.6) | 13 (23.6) | 5.0 (−7.35, 17.2) |

Data are expressed as mean (SE) or number (%). The difference in the mean or percentage of the variables between impaired glucose tolerance and impaired fasting glucose. CI = confidence interval, IGT = impaired glucose tolerance, IFG = impaired fasting glucose, BMI = body mass index.

[†] Age-adjusted means were calculated using general linear models.

* $P < 0.05$.

** $P < 0.01$.

### 3.2. *Reverting to NGT over time*

During 750 (138 men and 612 women) person-years of follow-up, 114 (30.8%) participants (22 (31.0%) men and 92 (30.8%) women) converted to NGT. The overall improvement rate was 15.2% (95% CI: 12.6, 17.8) per year. The improvement rates were similar in women (%15.0, 95% CI: 12.2, 17.9 per year) and men (%15.9, 95% CI: 9.8, 22.0). Of the 315 participants who had IGT at initial registration, 99 (31.4%) subsequently reverted to NGT at a rate of 16.2% (95% CI: 13.3, 19.1) per year. Of the 55 participants who had IFG at initial registration, 15 (27.3%) improved to NGT, giving an improvement rate of 10.9% (95% CI: 5.7, 16.1) per year.

### 3.3. *Predictors of reverting to NGT*

Baseline characteristics of the 114 (30.8%) participants reverted to NGT were compared with 256 (69.2%) who remained glucose intolerant, including those progressing to diabetes (Table 3). Those who reverted to NGT had lower age-adjusted mean fasting glucose, PG at 30, 60 min, BMI and $HbA_{1c}$. The mean (SD) age was 43.3 (6.1) years for those reverted to NGT and 43.5 (7.0) years for those remained glucose intolerance.

Age-adjusted mean WC, HC, and proportion of obesity and MetS were lower in those who reverted to NGT than those not reverted, but our data are limited in power to detect the impact of these variables on altered glucose metabolism.

As shown in Table 4, the BMI, WC, HC and weight more decreased among participants improved from glucose intolerance to NGT than those remained glucose intolerance. Participants who reverted to NGT consistently showed lower PG levels through the follow-up. Between baseline and the end of follow-up the cholesterol, LDL and triglyceride decreased among participants reverted to NGT, whereas increased in those not reverted. The groups were of similar age and gender distribution.

To determine the contribution of baseline variables with glucose tolerance at follow-ups, NGT vs. glucose intolerance, as the dependent variable a Cox proportional hazard model was performed to test 11 predictor variables: age, systolic BP, total cholesterol, HDL and LDL, triglyceride, fasting and 2-h PG, BMI, WC, all included as continuous variables, and gender. Lower baseline fasting PG (HR 1.02, 95% CI: 1.01, 1.04) and 2-h (HR 1.02, 95% CI: 1.002, 1.01) PG concentrations remained significant and independent predictors of reverting to NGT.

## 4. Discussion

In this cohort study, FDRs of patients with type 2 diabetes with IGT and IFG at baseline show 16.2% and 10.9%, per year conversion to NGT. Lower baseline fasting, 2-h PG, and changes in BMI, WC, glucose and lipids predicted reversal to NGT at 2 years follow-up. To the best of our knowledge, this is the first study to report on conversion rates from glucose intolerance to NGT in FDRs of people with type 2 diabetes. As with previous studies in general population, we found that a significant proportion of glucose intolerance individuals return to NGT over time [22,26,27,29]. Conversion rates to NGT from IFG and IGT in general populations have been examined in different populations [20,22–24]. Estimates of

**Table 3 – Age, age-adjusted mean (SE) and proportion characteristics[†] of first-degree relatives of patients with type 2 diabetes reverting to normal glucose tolerance or remaining glucose intolerance at follow-up, the Isfahan Diabetes Prevention Study.**

| Baseline characteristic | Reverted ($n$ = 114) | Not reverted ($n$ = 256) | Difference (95% CI) |
|---|---|---|---|
| Age (year) | 43.3 (0.6) | 43.5 (0.4) | −0.2 (−1.69, 1.29) |
| Weight (kg) | 72.8 (1.0) | 75.1 (0.7) | −2.3 (−4.71, 0.11) |
| Height (cm) | 158.3 (0.7) | 158.4 (0.5) | −0.1 (−1.78, 1.58) |
| Waist circumference (cm) | 89.2 (0.8) | 90.7 (0.5) | −1.5 (−3.43, 0.43) |
| Hip circumference (cm) | 107.8 (0.9) | 109.5 (0.6) | −1.7 (−3.75, 0.35) |
| Body mass index (kg/m$^2$) | 29.0 (0.4) | 30.0 (0.3) | −1.0 (−1.79, −0.01)* |
| Follow-up duration (year) | 2.0 (0.08) | 2.0 (0.06) | 0.0 (−0.20, 0.20) |
| Fasting glucose baseline (mg/dl) | 97.3 (1.0) | 103.9 (0.7) | −6.6 (−9.03, −4.17)*** |
| Plasma glucose 30 min (mg/dl) | 152.6 (2.8) | 165.8 (1.9) | −13.2 (−19.9, −6.49)*** |
| Plasma glucose 60 min (mg/dl) | 166.7 (3.6) | 186.4 (2.4) | −19.7 (−28.2, −11.4)*** |
| Plasma glucose 120 min (mg/dl) | 150.4 (2.4) | 154.6 (1.6) | −4.2 (−9.99, 1.59) |
| $HbA_{1c}$ (%) | 5.0 (0.09) | 5.2 (0.06) | −0.2 (−0.49, −0.01)* |
| Cholesterol (mg/dl) | 200.2 (3.9) | 202.6 (2.7) | −2.4 (−12.10, 6.88) |
| LDL-cholesterol (mg/dl) | 119.9 (3.3) | 119.8 (2.3) | 0.1 (−7.92, 8.12) |
| HDL-cholesterol (mg/dl) | 46.5 (1.2) | 46.5 (0.8) | 0.0 (−2.74, 2.74) |
| Triglyceride (mg/dl) | 174.0 (10.6) | 184.3 (7.1) | −10.3 (−35.7, 14.90) |
| Systolic BP (mmHg) | 115.1 (1.6) | 116.5 (1.1) | −1.4 (−5.20, 2.40) |
| Diastolic BP (mmHg) | 73.8 (1.3) | 75.4 (0.9) | −1.6 (−4.60, 1.40) |
| Men, no. (%) | 22 (19.3) | 49 (19.1) | 0.2 (−8.54, 8.86) |
| Obesity (BMI $\geq$ 30), no. (%) | 44 (39.3) | 113 (44.3) | −5.0 (−16.40, 5.23) |
| Metabolic syndrome, no. (%) | 27 (23.7) | 76 (29.7) | −6.0 (−15.6, 3.60) |

Data are expressed as mean (SE) or number (%). The difference in the mean or percentage of the variables between those who did or did not reverted to normal glucose tolerance. CI = confidence interval, BP = blood pressure, BMI = body mass index.

[†] Age-adjusted means were calculated using general linear models.

* $P < 0.05$.

** $P < 0.01$.

**Table 4 – Age-adjusted changes over time in subjects who did or did not reverted to normal glucose metabolism during mean 2 years follow-up period.**

| Characteristic | Change from baseline to final assessment | | Difference (95% CI) |
|---|---|---|---|
| | Reverted ($n$ = 114) | Not reverted ($n$ = 256) | |
| Waist circumference (cm) | −1.8 (0.4) | −0.5 (0.3) | −1.3 (−2.26, −0.34)* |
| Hip circumference (cm) | −2.3 (0.4) | −1.1 (0.3) | −1.2 (−2.20, −0.20)* |
| Weight (kg) | −3.1 (0.4) | −1.3 (0.2) | −1.8 (−2.64, −0.96)* |
| Body mass index (kg/m$^2$) | −1.3 (0.1) | −0.5 (0.1) | −0.8 (−1.14, −0.46)*** |
| PG baseline (mg/dl) | −8.1 (1.5) | 6.5 (1.0) | −14.6 (−18.20, −11.00)*** |
| PG 30 min (mg/dl) | −20.4 (3.7) | −5.5 (2.7) | −14.9 (−24.00, −5.85)** |
| PG 60 min (mg/dl) | −25.5 (4.0) | 0.2 (2.7) | −25.7 (−35.00, −16.40)*** |
| PG 120 min (mg/dl) | −45.5 (3.5) | −1.2 (2.3) | −44.4 (−52.60, −36.20)*** |
| $HbA_{1c}$ (%) | −0.03 (0.08) | 0.08 (0.6) | −0.11 (−0.31, 0.09) |
| Cholesterol (mg/dl) | −4.9 (3.5) | 16.0 (2.4) | −20.9 (−29.1, −12.7)*** |
| LDL-cholesterol (mg/dl) | −3.3 (3.4) | 12.7 (2.4) | −16.0 (−24.10, −7.90)*** |
| HDL-cholesterol (mg/dl) | 1.4 (1.1) | 0.4 (0.7) | 1.0 (−1.59, 3.59) |
| Triglyceride (mg/dl) | −20.7 (8.7) | 8.2 (5.9) | −28.9 (−49.6, −8.26)** |
| Systolic BP (mmHg) | 3.2 (5.5) | 5.9 (3.8) | −2.7 (−15.70, 10.30) |
| Diastolic BP (mmHg) | 5.1 (1.4) | 2.1 (1.0) | 3.0 (−0.35, 6.35) |

Data are expressed as mean (SD). The difference in the means of the variables between reverted and not reverted to normal glucose. PG = plasma glucose. CI = confidence interval.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

conversion to NGT from IFG and IGT will depend upon the methodological factors, the definition of the IGT, and IFG used, unknown time spent with IFG and IGT, follow-up period and the composition of the community examined by age and gender, making comparisons between studies of limited values. The proportion of glucose intolerance individuals who reverted to NGT in this study is almost compatible with most of that observed in other studies in general populations [1,22,29] ranged from 16.8% to 62.8% with observation period of between 6 weeks and 10 years [1,16–29].

Our data indicate that when glucose intolerance improves to NGT, lipids and body size also improved. They had serum triglyceride concentrations, serum LDL and cholesterol concentration, weight, WC, HC, BMI and glucose levels that were significantly different at baseline. This reversibility of factors with improvement of glucose tolerance is compatible with that observed in Singapore [22]. We were particularly interested in the role of weight loss. In our study, participants who reverted to NGT loss much more weight than those remained glucose intolerance. Weight loss appears to be the most important component of lifestyle predicting restoration of NGT. Several studies have shown that change in BMI was a significant predictor [21,22,25,26] of reversal to NGT. Similarly, change in WC was a significant predictor for restoration of NGT.

We found that several features of the MetS are reversible and change with improvement in glucose tolerance. This suggests that weight loss, improve lipids levels make a significant contribution to the subsequent improvement to NGT.

Previous studies have shown that individuals with glucose intolerance (even if they revert to NGT) may be at increased risk of future diabetes [1,22] and warrant continued surveillance. Our data also suggest that such surveillance, and possibly lifestyle intervention, may be important for the prevention of worsening to more advanced stage of impaired glucose metabolism.

It seems likely that the high improvement rates within a short time in our high-risk population may be due to being given detailed information and education about diabetes prevention as part of the IDPS, and this may have influenced our reported findings. The improvement in glucose tolerance with lifestyle change may be the result of improved beta-cell function along with enhanced insulin sensitivity.

The mechanisms underlying the conversion of glucose intolerance to NGT in FDRs of patients with type 2 diabetes are not entirely clear. The variability in OGTT results may be accounted for by the phenomenon of regression to mean [36,37], awareness in the population studied [36–38], or factors known to impair glucose tolerance such as drugs, change in body weight or diet, emotional or physical stress [1]. In this study improvements in glucose tolerance do not appear to be artifacts of repeat testing, since these FDRs had lost much more weight on follow-up than those who remained glucose intolerance.

In agreement with Alvarsson et al. [14] a lower fasting and 2-h PG concentrations was predictive value for reverting to NGT.

The strengths of present study include the prospective cohort design, the sample consisting of both men and women of a wide age range, diagnosis of glucose intolerance based on standard OGTT, and information on potential determinants of reverting to NGT. Selection and information bias is considered unlikely by virtue of the prospective design. Our study was addressed to individuals at increased risk of developing type 2 diabetes, because they had FDRs with the disease. The multiple examinations with OGTTs make the improvement rates very accurate. Even though the study included more than 350 participants with glucose intolerance that were thoroughly examined and followed up, the follow-up period of 2 years may be controversial. Due to the still conflicting results in assessing conversion rate prediction a long-term follow-up in a large cohort could therefore further contribute to a clarification of the question. Subjects reverting to NGT show a greater decline in BMI, WC, and lipids which suggests a more pronounced improvement in insulin sensitivity and/or beta-cell function. To better estimate conversion to NGT, it appears necessary to measure insulin. Unfortunately, the data used here do not allow for an empirical test of this speculation. Further research would be useful to examine what sensitivity measure of insulin plays a role in the conversion rate to NGT of FDRs of patients with type 2 diabetes.

In conclusion, the findings of this study illustrate the predictors of reverting from IGT and/or IFG to NGT in FDRs of patients with type 2 diabetes in Iran. Lower fasting, 2-h PG at baseline, change in BMI, WC, and lipids predicted reversal to NGT at 2 years follow-up.

## Conflict of interest

The authors declared no conflict of interest.

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