Lifestyle factors and reversion to normoglycaemia by prediabetes type in PREDAPS study.

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Abstract

Background: Healthy lifestyle interventions and drug therapies are proven to have a positive preventative influence on normal glucose regulation in prediabetes; however, there is little evidence to support the role of these factors according to the various stage of the prediabetes state. Aims : This study aims to investigate the role of lifestyle factors on the reversion to normal glucose regulation according to the different stage of the prediabetes state based on most up-to-date American Diabetes Association (ADA) guidelines. Design and Setting: Observational prospective cohort study. The Cohort study in Primary Health Care on the Evolution of Patients with Prediabetes from 2012-2015

Methods: A total of 1184 individuals aged 30 to 74 years old were included and classified based on the ADA in three mutually exclusive groups using either fasting plasma glucose (FPG) levels (from 100-125 mg/dl, FPG group), (HbA 1c (5.7%–6.4%, HbA1c group) or both impaired parameters group. Information on lifestyle factors and biochemical parameters were collected at baseline Reversion to normal glucose regulation was calculated at third year of follow-up. Relationship of lifestyle factor and type of prediabetes with reversion were estimated using odds ratios (ORs) with 95% confidence intervals (CIs) adjusting by different groups of confounders.

Results: Proportion of reversion rates were 31% for FPG group, 31% for HbA1c group and 7.9% for both altered parameters group, respectively. Optimal life style factors such as BMI<25 kg/m 2 [OR (95% CI): 1.90 (1.20-3.01)], high adherence to Mediterranean diet 1.78 (1.21-2.63) and absence of abdominal obesity 1.70 (1.19-2.43) were the strongest predictors for reversion to normal glucose. ORs of reversion to normal glucose were 4.87 (3.10-7.65) for FPG group and 3.72 (2.39-5.78) for HbA1c group, taking as reference those with both impaired parameters. These estimates remained almost the same after further adjustment for biochemical parameters and lifestyle factors.

Conclusions: Although optimal lifestyle factors showed to be a positive predictor for reversion to normal glucose regulation, they do not seem to explain the differences according to the type of prediabetes.

Background

The global prevalence of diabetes among adults aged 18 and beyond, has risen from 4.7% in 1980 to 8.5% in 2014, representing almost 422 million people by 2014 [1]. Together with this trend, mortality of diabetes has scaled up to be positioned in the eight causes of dead rank worldwide [2]. Risk factors for developing diabetes type 2 have been well established and characterized [3–5], therefore interventive measures to reduce the burden of this disease has been widely spread among the different healthcare systems. In addition, several studies have concluded that adherence to a healthy lifestyle (including healthy diet, smoking cessation, increase in physical activity, reduction in alcohol consumption, and reduction in body mass index (BMI)) at age 50–75, is associated with six to ten years increase in life years and significant improvement of quality of life as well as a reduction in prevalence of major chronic

diseases (including cancer, cardiovascular diseases and diabetes) compare to individuals with no vast improvement in lifestyle [6–7].

Prediabetes status has been associated with a higher risk of developing diabetes type 2. This stage is characterized by either an impaired fasting plasma glucose (IFG) or impaired glucose tolerance (IGT), or elevated glycated haemoglobin A1c (HbA1c) depending on the established diagnostic criteria [8]. Prior research on this topic highlight optimal lifestyle factors and drug therapies (majority oral antidiabetic medications) implementations as effective predictive positive factors to conversion to normal glucose regulation in subjects with prediabetes [4, 9–10]. However, those interventions do not seem to play the same role depending on the type of prediabetes. For example, some studies have found a better response to glucose regulation after applying lifestyle modifications only in individuals with IGT [11]. In addition, a recent study observed how individuals with HbA1c levels in range of prediabetes were less likely to revert to normal glycaemia after physical activity recommendations [12].

This apparent heterogeneous association, between optimal lifestyles and reversion to normal glycaemia regulation according prediabetes type, could be the cornerstone for individualized prevention strategies in subjects with prediabetes. However, there is little evidence on how healthy lifestyle factors can explain the variation in the proportion of patients reverting to normal glucose regulation according to type of prediabetes. In order to develop a better understanding of the following matter, this study aims to evaluate the key role of lifestyle factors on predicting reversion to normal glycaemia by type of prediabetes using a prospective cohort of individuals with prediabetes followed up by primary care physicians in Spain.

Methods

Study design

The Cohort study in Primary Health Care on the Evolution of Patients with Prediabetes (PREDAPS Study) is a prospective study encompassing two cohorts of patients: those with prediabetes status and those free of prediabetes and diabetes. Details on information and design published previously by the same authors [13]. Briefly, this prospective study conducted at the primary care setting, started in 2012. To be member of the prediabetes cohort individuals aged 30 to 74 years old were included when meeting the following prediabetes criteria based on the definition established by American Diabetes Association [14] using FPG and HbA1c parameters. First group, namely i) isolated FPG group, included all individuals with HbA1c <39 mmol/mol (<5.7%) and FPG 100–125 mg/dl, ii) isolated elevated HbA1c group, included all individuals with HbA1c 39–47 mmol/mol (5.7%–6.4%) and FPG<100 mg/dl and iii) both altered parameters group, included all individuals with HbA1c 39–47 mmol/mol (5.7%–6.4%) and FPG 100–125 mg/dl. Participants aged 30 to 74 years old with HbA1c <39 mmol/mol (<5.7%) and FPG <100 mg/dl were assigned to the normoglycaemia cohort. Individuals with the following criteria were excluded (to be members) from the study cohort: diabetes, terminal disease, pregnancy, surgery, or hospital admission in the previous 3 months at study entry, or any hematologic disease, which could alter HbA1c values. The

study was classified by the Spanish Drug and Health Product Agency as a Non-Interventional (Observational) Post-Authorization Study, and the protocol was approved by the Parc de Salut Mar Clinical Research Ethics Committee in Barcelona. A total of 2022 individuals gave their written informed consent for participation: 1184 subjects with prediabetes and 838 without impaired glucose metabolism.

The present study analysed the relationship between lifestyle and other variables measured at baseline and the situation of reversion to normal glycaemia in the third year of follow-up among the cohort of subjects with prediabetes. Thus, out of 1184 subjects with prediabetes, a total of 948 (80.1%) attended their third follow up visit and were retained to be members of the final cohort, therefore remaining patients were excluded. Reversion to normal glucose regulation, was considered if FPG and HbA1c values were FPG <100 mg /dl and HbA1c <39 mmol/mol (<5.7%), respectively, at third year of follow up.

Data Collected

At baseline, information on biographical data, family and personal history of diabetes, smoking, alcohol consumption, diet, physical activity, drug treatment, social support and socio-economic position was obtained from each participant's clinical history and from the personal interview conducted by the physician at their practices. During the medical visit a physical examination was performed, which included anthropometry and determination of blood pressure. Similarly, blood and urine analyses were requested to determine FPG, HbA1c, lipid profile, transaminases, blood count, iron levels and renal function. Of note, all variables were treated as categorical data

Smoking habit was classified into three mutually exclusive categories: current smoker, former smoker, and non- smoker. Individuals were asked to state which of the following alternatives best reflected their alcohol consumption frequency: never drinker, former drinker, occasional drinker, or daily drinker. For the present analysis individuals were classified into non-drinkers, occasional drinkers and daily drinkers. Physical activity data were collected based on the frequency –number of times in the last two weeks- and amount –mean time in minutes for each session as well as different types of physical activity, and, on the basis of the data collected, the minutes per week of physical activity performed by each participant were estimated. Subjects were classified into two categories to their compliance with the World Health Organization (WHO) physical activity recommendations -accumulate at least 150 minutes per week of moderate aerobic activity or 75 minutes per week of vigorous aerobic activity-, or an equivalent combination of moderate and vigorous physical activity [15].

Adherence to the diet was estimated through an adaptation of the score used by *Panagiotakos* in the ATTICA study [16]. In each of the 20 types of food investigated, research subjects were asked about the following frequency consumption options: daily consumption, ≥ 3 times / week, 1–2 times / week, <1 time / week, never or almost never. A score of 0 was assigned to a less healthy consumption and 4 to the healthiest consumption of each food categories. A score of 0 is considered minimum adherence, compared to 80, which would be maximum adherence. Adherence to the Mediterranean diet was grouped into three categories low (0–53 points), medium (54–59 points) and high (60–80 points).

Overweight and general obesity was defined as a Body Mass Index (BMI) ≥25g/m^2, and abdominal obesity as a waist circumference ≥102 cm in men and ≥88 cm in women. Hypertension was defined as systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg, or current use of antihypertensive treatment or having a personal history of hypertension. Hypercholesterolemia was defined as total serum cholesterol ≥250 mg/dl, high-density cholesterol level (HDL-C) of as <40 mg/dl in men and <50 mg/dl in women, and hypertriglyceridemia as serum level of triglycerides ≥200 mg/dl

Statistical analysis

A descriptive analysis of the distribution of demographic characteristics, lifestyle variables, obesity, and hypertension and biochemical parameters, according to type of prediabetes was performed using the chi-square test (categorical variables). Then it was calculated the percentage of subjects who reverted to normal glycaemia according to these variables and types of prediabetes. The relationship between demographic characteristics, lifestyle variables, obesity, hypertension and biochemical parameters and the reversion to normal glycaemia was estimated by odds ratio (OR) adjusted for age and sex. Relationship between type of prediabetes and the reversion to normal glycaemia was estimated using three sequential models: adjusting for age and sex (Model A); hypertension, hypercholesterolemia, HDL levels and triglycerides (Model B), and alcohol consumption, smoking, BMI, abdominal obesity, physical activity, adherence to Mediterranean diet (Model C). Each successive model included the factors from the previous model. Finally, diagnostic criteria's of prediabetes was subdivided using as cut-off levels FPG<110 and≥110mg/dl and HbA1c <42 and ≥42mmol/mol (<6 and ≥6%), respectively, and the relationship between subtype of prediabetes and the reversion to normal glycaemia was also estimated by models A, B y C. Statistical analyses were performed using the STATA package version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Baseline characteristics

Among our cohort of prediabetes, mean age was 58.7 years (median: 60 years). Amongst them, 21% of patients were classified as having isolated impaired FPG, 27.6% had isolated elevated HbA1c levels and 50.9% had both altered parameters. *Table 1* shows the baseline characteristics of study cohort according to type of prediabetes. There was an inverse proportion of men and women according to each prediabetes criteria, while 61% of those with isolated impaired FPG were men, corresponding percentages by isolated elevated HbA1c and both parameters were 38.9% and 50.3%, respectively (p<0.001). Distribution of age was similar within groups, although those with isolated IFG tended to be younger. In terms of alcohol consumption, the proportion of daily drinkers were 29% among those with both altered parameters compared to 19.5% among those with isolated elevated HbA1c and 34% among those with isolated impaired FPG. Those with both altered parameters had higher proportions of BMI >25 kg/m^2 and abdominal obesity. There were no differences in distribution of remaining lifestyle factors as smoking,

physical activity and adherence to diet. Those with both altered parameters had a higher frequency of hypertension and triglycerides levels and there were no differences in distribution of hypercholesterolemia or HDL levels.

Reversion rates according to type of prediabetes

At third year of follow up, there were a total of 165 (17.4%) patients who reverted to normal glucose regulation. When stratifying by type of prediabetes, the proportion of patients reverting to normal glycaemia defined by both -HbA1c and FPG criteria had the lowest proportion of reversion (7.9%) compared with those defined with isolated impaired FPG (31.0%) or isolated elevated HbA1c (24.4%), respectively (Figure 1). We subdivided the diagnostic criteria of prediabetes using as cut-off levels FPG<110 and >110mg/dl and HbA1c <42 and ≥42mmol/mol (<6 and ≥6%), respectively. Individuals with HbA1c levels ≥42mmol/mol (<6%) had the lowest reversion rates (3.2% for those with FPG: 100–125 mg/dl and 8.7% with FPG <100mg/dl), while those with isolated FPG <110 mg/dl and isolated HbA1c <42 mmol/mol (<6%) obtained the highest reversion rates (40.7% and 32.9%) (Figure 2).

Factors associated with the reversion to normoglycemia

Table 2 shows the percentage of reversion according to each baseline characteristic factor as well as the OR of reversion. We did not observe any association with sex. There was a trend towards a decreased likelihood of reversion with the increase in age. Lifestyle factors such as BMI<25 kg/m^2 [OR 1.90 (95% CI:1.20–3.01)] compared to BMI>25, absence of abdominal obesity [OR 1.70 (95% CI 1.19–2.43)] compared of having a waist circumference ≥102 cm in men and ≥88 cm in women, a high adherence to Mediterranean diet [OR 1.78 (95% CI 1.21–2.63)] compared to having low/median adherence and following the OMS recommendations on physical activity [OR 1.48 (95% CI:1.04–2.10)] compared to not following them showed to be positive predictive factors associated with reversion to normal glycaemia. Not having hypertension shown to be associated with reversion to normoglycaemia, and there was no association with biochemical parameters such as hypercholesterolemia, HDL low levels or hypertriglyceridemia

Role of Lifestyle factors on reversion according to type of prediabetes

Compared with participants with both FPG and HbA1c criteria, when adjusting by age and sex, the OR of reversion of prediabetes was 4.87 (95% CI: 3.10–7.65) among those with isolated impaired FPG and 3.72 (95% CI: 2.39–5.78) for those with isolated elevated HbA1c.When adding biochemical parameters as well as hypertension (Model B), OR remained almost constant: 4.78 (95% CI: 3.03–7.55) and 3.59 (95% CI: 2.30–5.60), respectively. Finally, when including lifestyle factors (Model C), OR did remain almost the same: 4.52 (95% CI: 2.84–7.18) for isolated impaired FPG group and 3.43 (95% CI: 2.17–5.42) for

isolated elevated HbA1c group (Table 3). Also, when subdividing prediabetes cohort according to levels of FPG and HbA1c, the OR in de Model C which was similar to OR in the Model B. Taking as reference those with HbA1c levels ≥42 mmol/mol (≥6%) and FPG 100–125 mg/dl, the OR for reversion after adjusting for all factors (Model C) were as follows: isolated FPG <110 mg/dl: 18.21 (95% CI: 8.08–41.06), isolated FPG ≥110 mg/dl: 5.75 (95% CI: 2.30–14.37), isolated HbA1c <42 mmol/mol (<6%): 13.34 (95% CI: 6.03–29.52), isolated HbA1c ≥42 mmol/mol (≥6%): 2.70 (95% CI: 0.97–7.51), and HbA1c <42 mmol/mol (<6%) and FPG 100–125 mg/dl: 4.36 (95% CI: 1.94–9.80).

Discussion

Main Findings

The current prospective cohort study included a total of 948 individuals with a prediabetes status. At the third year of follow-up, compared with the group of subjects with both altered parameters, FPG and HbA1c, the reversion to normal glucose regulation was almost four times higher in subjects with isolated elevated HbA1c and almost five times higher in subjects with isolated impaired FPG.

Strengths and limitations

This study has several strengths and limitations that deserve some comment. Several strengths and limitations should be acknowledged. To best of our knowledge, this is the first study evaluating the role of optimal lifestyle factors in the reversion to normal glucose regulation according type of prediabetes. Our study highlights the feasibility of conducting a prospective observational study, with data collected nation-wide by primary care physicians during routine clinical practice. Although the data were collected extensively and measured at fixed predetermined points (baseline data collection and regular follow-ups) the researchers were unable to determine a time-dependent variable. being unable to time-dependent variables. However, the vast majority of the factors considered in the present study are chronic conditions or long-term lifestyle factors not susceptible to a fast variation within the follow-up during the study period. Regarding to lab data, analytical determinations of FPG, HbA1c and covariates were performed at different laboratories. This fact could result in some source of misclassification. Of note, since each patient was assigned to the same laboratory during the follow-up, this limitation should be minor and expected to be non-differential in relation to the outcome, as it is unlikely that the reversion could be related to the methods employed by specific laboratories. Several items included in the survey a source of misclassification might not be ruled out. To create the adherence to Mediterranean diet variable we used the food frequency questionnaire is the most commonly used instrument to assess past dietary intake in epidemiological studies. Although 24-h dietary recall and dietary records have been used to measure usual dietary intake, both instruments are expensive and unrepresentative of usual intake and therefore, inadequate for the assessment of past dietary intake (17–18). The food frequency questionnaire is the most commonly used instrument to assess past dietary intake in epidemiological studies. The (FFQ) used here, based on five food categories, is a validated instrument to asses dietary patterns (19–20) and

it has been observed that the information it provides is a good predictor of mortality in diabetic and non-diabetic subjects (21). The instrument of measurement of physical activity here allows evaluating compliance with the recommendations of the American College of Sports Medicine (22) and the World Health Organization (23). This instrument may overestimate compliance with the recommendations because it measures the periodical activity habit such as a number of times that physical activity was performed in the last two weeks and therefore is not based on daily performances.However, it is unlikely that this overestimation is differential with respect to the type of prediabetes of the subjects. Finally, since reversion to normal glycemia might not be a permanent and chronic condition (i.e. some subjects might change from first visit to third) we decided to use as a cutoff point the third visit of follow up to ensure a minimum time-lapse to measure the reversion to normal glycemia. Therefore, the subjects who did not reach the third visit were excluded. The percentage of dropout was 21% in subjects with prediabetes defined by both HbA1c and FPG criteria, 16% in subjects defined by only HbA1c and 19% in subjects defined by only FGP. When evaluating the baseline characteristics of the dropped-out patients (N = 236 (19.9%), there were no major substantial differences among both groups (Supplement table 1). Therefore, selection bias in our study should be minor.

Comparison with existing literature

Despite there are prior studies evaluating the proportion of reversion to normoglycaemia, all them were heterogeneous in design, duration of follow-up and criteria definition yielding a broad range of reversion rates [24–28], and only few did it according to prediabetes status criteria [12, 29]. The latter, a Japanese study [29] using four prediabetes subgroups according to elevated HbA1c and/or FPG, observed a greater proportion of reversion rates among those with elevated HbA1c levels. In contrast, our results showed an opposite trend resulting in lower rates for individuals with HbA1c levels above 42 mmol/mol (6.0%) regardless FPG levels, similar to the results provided by a British study [12].

A potential source of misclassification when classifying patients according to FPG levels cannot be ruled out. While FPG is subjected to not only intra-individual variability but also daily variation levels [30], HbA1c reflects average plasma glucose over the previous eight to 12 weeks [31] acting as a more established parameter. In the current study, and focusing on those classified with isolated impaired FPG levels, we found how among those with FPG levels <110 mg/dl (representing >50% of this group) presented the highest reversion rate, and 2.3-fold times higher likelihood of reversion compared to those with FPG ranging from 110–125 mg/dl, respectively. If any substantial impact of misclassification, we would not be able to see this difference.

A recent study, that applied the same prediabetes criteria than ours, observed how individuals who reverted to normal glycaemia regulation after five years of follow up, had a low insulin resistance and optimal beta-cell function at baseline [32]. Following this reasoning, is probable, that in our study population, individuals with HbA1c ≥42mmol/mol (≥6%) at baseline had an increased insulin resistance

and/or a decreased beta cell function, which might explained the lowest reversion rates found. However, we were not able to measure such physiological markers.

In the present study, baseline characteristics such as age less than 50 years, normal weight, absence of abdominal obesity, physical activity, adherence to Mediterranean diet and absence of hypertension have been associated with a higher likelihood to normal glucose regulation. There are prior studies evaluating reversion to glucose regulation using an interventional design mainly focus on optimal lifestyle actions in a prediabetes population. However, only few are focused on this relationship using a fixed period (i.e. baseline levels). The vast majority, although not all [12, 33], draw similar conclusions than ours [3, 24–25, 27–28, 34]. Both, obesity and body fat distribution, are critical factors to decrease insulin sensitivity and B cells function [35]. In contrast, physical activity causes increased glucose uptake into active muscles balanced by hepatic glucose production and it improves insulin action resulting in preventing insulin resistance [36]. In addition, there is evidence that a low-glycaemic-index diet, such as Mediterranean, improves insulin sensitivity and prevents from diabetes [37]. It is therefore probable that individuals reverting to normal glucose regulation followed an optimal lifestyle behaviour long time before baseline state.

Implications for research and/or practice

There is a gap in knowledge about the extent to which healthy lifestyles explain the reversion to normal glucose regulation, according to the type of prediabetes. The current study found that adjustment for lifestyles did not modify markedly the magnitude of association between type of prediabetes and reversion, which suggests that the excess restore to normal glucose in individuals with isolated impaired FPG or isolated elevated HbA1c cannot be explained via these factors. Therefore, our findings suggest that beyond optimal lifestyles, FPG and HbA1c could be in themselves key markers to revert to normal glycaemia in subjects with prediabetes, especially the FPG level below 110 mg/dl and the HbA1c level below 42 mmol/mol (6.0%).

The criteria of prediabetes are still a controversial topic, based on multiple changes in its definition. Controversy especially lies on the cut-off value levels to define FPG levels <110 mg/dl [38–39]. Keeping in mind that almost half of the subjects with those FPG levels reverted to normal glycaemia, this might lead into an overestimation of the true prevalence of this status. Of note, those patients would not be the specific target for intensification of optimising lifestyle factors and other actions such as initiating antidiabetic therapy. In addition to existing doubts about the adequacy of FPG levels below 110 mg/dl to define prediabetes, our findings add new arguments to this controversy given the limited role of optimal lifestyles in the differences to the reversion according to the type of prediabetes. Further studies evaluating reversion to normal glucose regulation and the role of optimal lifestyle factors, together with, clinical outcomes associated to prediabetes diagnostic criteria, are warranted to not only harmonize definitions on prediabetes but also to better identify specific subjects with a low probability of normalizing glycaemia levels.

In conclusion, optimal lifestyle factors showed to be a positive factor to reversion to normoglycaemia after three years of follow up in our prediabetes cohort however, they do not seem to explain differences in the reversion to normal glucose regulation according type of prediabetes.

Declarations

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Sanofi and Novartis were both financial investors (for the development of the data collection platform, the meetings of researchers, and the monitoring of information collected at baseline).

Declaration of interest

The authors declare that they have no conflict of interest. Sanofi and Novartis had no role in the study design, analysis and interpretation of data, writing of the manuscript, nor the decision to submit the manuscript for publication.

Author contribution statement

CG-G and LC-S originated and designed the study, contributed to the analysis of the data and to the drafting of the paper. FJ-N, MM, FJS, JD-ES, SA and RS collected data of the study and contributed to the interpretation of the results and to the drafting of the paper. FJGS and RS collected data of the study and coordinated the writing of the article. RA, and ER contributed to the analysis of the data and to the drafting of the paper. All authors contributed to the final version of the article. All authors have seen and approved the final version. ER is the guarantor of the study.

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Tables

Table 1 Baseline characteristics of study cohort individuals according type of prediabetes.

Characteristics	Isolated impaired FPG FPG:100-125 mg/dl and HbA1c: <39 mmol/mol		Isolated elevated HbA1c FPG: <100 mg/dl and HbA1c:39-47 mmol/mol		Both altered parameters FPG:100-125 mg/dl and HbA1c:39-47 mmol/mol		*p value* *group1 vs group 2*	*p value* *group1 vs. group 3*	*p value* *group 2 vs. group 3*
	N	%	N	N	N	%			
Sex							<0.001	0.010	0.003
Women	79	38.9	240	240	240	49.7			
Men	124	61.1	243	243	243	50.3			
Age							0.181	<0.001	0.129
30-49 years	46	22.7	60	60	60	12.4			
50-64 years	104	51.2	241	241	241	49.9			
65+ years	53	26.1	182	182	182	37.7			
Smoking							0.032	0.050	0.403
Current smoker	28	13.8	77	77	77	15.9			
Former smoker	96	47.3	180	180	180	37.3			
Never smoker	79	38.9	229	229	229	46.8			
Alcohol consumption							0.001	0.121	0.018
Daily drinker	69	34	140	140	140	29			
Ocassionally drinker	84	41.4	187	187	187	38.7			
Never drinker	50	24.6	156	156	156	32.3			
BMI							0.516	<0.001	<0.001
Overweight/Obese (>25 kg/m^2)	169	83.3	448	448	448	83.3			
Normal weight (up to 25 kg/m^2)	34	16.7	35	35	35	16.7			
Obesity abdominal							0.536	<0.001	<0.001
Waist ≥ 88/102 cm	119	58.6	362	362	362	74.9			
Waist <88/102 cm	84	41.4	121	121	121	25.1			

Physical Activity							0.833	0.443	0.275
Do not follow OMS recommendations	251	55.2	112	112	112	52.0			
Follow OMS recommendations	91	44.8	232	232	232	48			
Adherence to Mediterranean diet							0.006	0.931	0.031
Low	51	25.1	125	125	125	25.9			
Medium	98	48.3	236	236	236	48.9			
High	54	26.6	122	122	122	25.2			
Hypertension							0.161	0.007	<0.001
Yes	130	64.0	359	359	359	74.3			
No	73	36.0	124	124	124	25.7			
Hypercholesterolemia							0.061	0.199	0.379
Yes	112	55.2	292	292	292	60.5			
No	91	44.8	191	191	191	39.5			
Low HDL levels							0.684	0.044	0.084
Yes	38	18.7	125	125	125	25.9			
No	165	81.3	358	358	358	74.1			
Hypertriglyceridemia							0.872	0.008	0.002
Yes	47	23.2	161	161	161	33.3			
No	156	76.8	322	322	322	66.7			

*Chi square of heterogeneity

Table 2 Percentage of reversion to normal glucose regulation and odds ratio (OR) according to the characteristics of the subjects

Characteristics	Percentage of reversion	Odds ratio (95% confidence interval)*
Sex		
Women	16.7	1.00
Men	18.1	1.06 (0.75-1.49)
Age		
30-49 years	31.5	2.92 (1.82-4.69)
50-64 years	15.6	1.17 (0.78-1.76)
65+ years	13.6	1.00
Smoking		
Current smoker	17.2	1.00
Former smoker	17.8	1.23 (0.74-2.04)
Never smoker	17.1	1.19 (0.71-1.99)
Alcohol consumption		
Daily drinker	14.6	1.00
Occasionally drinker	19.9	1.33 (0.85-2.07)
Never drinker	16.6	1.10 (0.66-1.82)
BMI		
Overweight/Obese (>25 kg/m^2)	16.2	1.00
Normal weight (up to 25 kg/m^2)	26.1	1. 90 (1.20-3.01)
Physical Activity		
Do not follow OMS recommendations	14.9	1.00
Follow OMS recommendations	19.4	1.48 (1.04-2.10)
Adherence to Mediterranean diet		
Low/Medium	17.9	1.00
High	17.2	1.78 (1.21-2.63)
Obesity abdominal		
Waist >= 88/102 cm	14.8	1.00
Waist <88/102 cm	22.9	1.70 (1.19-2.43)

Hypertension		
Yes	14.7	1.00
No	23.1	1.53 (1.06-2.19)
Hypercholesterolemia		
Yes	17.3	1.00
No	17.5	1.02 (0.72-1.45)
Low HDL levels		
Yes	18.5	1.00
No	17.1	0.98 (0.65-1.47)
Hypertriglyceridemia		
Yes	14.6	1.00
No	18.5	1.38 (0.93-2.05)
* Sex and age adjusted odds ratio, except the odds ratios according sex and age All variables were considered and treated as categorical variables		

Table 3 Reversion to normal glucose regulation. Odds ratio (and 95% confidence interval) according prediabetes type and according prediabetes subtype.

	Model A	Model B	Model C
Prediabetes type			
Both altered parameters	1,00	1,00	1,00
Isolated elevated HbA1c	3.72 (2.39-5.78)	3.59 (2.30-5.60)	3.43 (2.17-5.42)
Isolated IFG	4.87 (3.10-7.65)	4.78 (3.03-7.55)	4.52 (2.84-7.18)
Prediabetes subtype			
HbA1C ≥42 mmol/mol and FPG 100–125 mg/dl	1,00	1,00	1,00
HbA1c<42 mmol/mol and FPG 100–125 mg/dl	4.54 (2.03-10.17)	4.46 (1.99-9.99)	4.36 (1.94-9.80)
Isolated HbA1c≥42 mmol/mol	2.81 (1.02-7.74)	2.75 (0.99-7.61)	2.70 (0.97-7.51)
Isolated HbA1c <42 mmol/mol	14.65 (6.73-31.91)	14.11 (6.44-30.94)	13.34 (6.03-29.52)
Isolated FPG≥110 mg/dl	6.18 (2.50-15.30)	6.03 (2.43-14.98)	5.75 (2.30-14.37)
Isolated FPG<110 mg/dl	19.76 (8.84-44.15)	19.28 (8.60-43.25)	18.21 (8.08-41.06)

Model A: Adjusted by sex and age

Model B: Model A plus hypertension, hypercholesterolemia, HDL levels and Triglycerides

Model C: Model B plus alcohol consumption, smoking, BMI, abdominal obesity, physical activity, adherence to Mediterranean diet

All variables were considered and treated as categorical variables

Figures

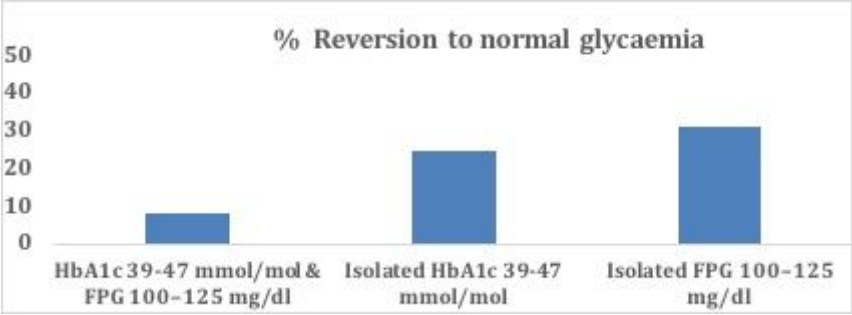

Figure 1

Proportion of patients reverting from prediabetes to normal glycaemia stratified by type of prediabetes.

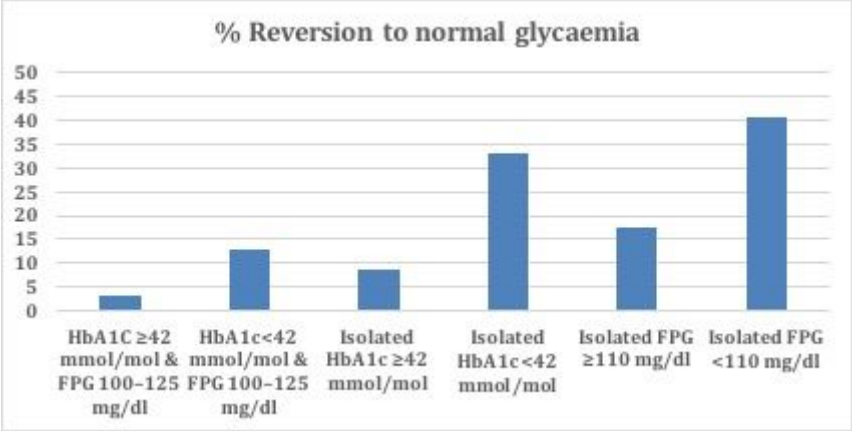

Figure 2

Proportion of patients reverting from prediabetes to normal glycaemia stratified by subtype of prediabetes

Supplementary Files

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