The Heterogeneity of Reversion to Normoglycemia According to Prediabetes Type is not Explained by Lifestyle Factors.

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Research Article

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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, little is known on the specific role that these factors play on reversion to normal glycemia according to type of prediabetes

Methods: We used data from the Observational prospective cohort study. The Cohort study in Primary Health Care on the Evolution of Patients with Prediabetes from 2012-2015. 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 (95% 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. However, those did not modify the ORs of reversion to normal glucose. Taking as reference those with both impaired parameters, subjects with FPG impairment (FP group) had an OR of 4.87 (3.10-7.65) and 3.72 (2.39-5.78) for HbA1c group. These estimates remained almost the same after further adjustment for biochemical parameters and lifestyle factors (4.55(2.84-7.28) and 3.09 (1.92- 4.97), respectively).

Conclusions: Optimal lifestyle factors showed to be a positive predictor for reversion to normal glucose regulation however, the differences of reversion risk according type of prediabetes are not explained by lifestyle factors.

Introduction

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]. In Spain the prevalence of diabetes in 2010 we 13.6% [2]. Moreover, the mortality of diabetes has scaled up to be positioned in the eight causes of dead rank worldwide [3]. Risk factors for developing diabetes type 2 have been well established and characterized [4-6], which has allowed to implement interventive measures to reduce the burden of this disease across different healthcare systems. As an example, 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), has been associated with six to ten years increase in life years and a significant improvement of quality of life. These implementations also resulted in a reduction in prevalence of major chronic diseases (including cancer, cardiovascular diseases and diabetes) compare to individuals with no vast improvement in lifestyle [7-8].

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 hemoglobin A1c (HbA1c) depending on the established diagnostic criteria [9]. Prior research on this topic highlights how optimal lifestyle factors and drug therapies (majority oral antidiabetic medications) implementations are effective predictive positive factors to conversion to normal glucose regulation in subjects with prediabetes [5, 10-11]. 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 [12]. 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 [13].

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.

Material And 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 with normal glycemia (i.e. non-prediabetes neither diabetes) with the attempt to study the progression, prognosis and behavior of prediabetes. Details on information and design published previously by the same authors [14]. 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 [15] using FPG and HbA1c parameters. First group, namely i) group 1 (isolated impaired FPG), included all individuals with HbA1c <39 mmol/mol (<5.7%) and FPG 100–125 mg/dl, ii) group 2 (isolated elevated HbA1c group), included all individuals with HbA1c 39-47 mmol/mol (5.7%–6.4%) and FPG<100 mg/dl and iii) group 3 (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 normoglycemia 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. 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 analyzed the relationship between lifestyle and other variables (i.e. including lifestyle factors and metabolic conditions) 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. The main causes of exclusion were the administrative assignment of the participants to another general practitioner, change of their place of residence and refusal to continue in the study. 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. The questionnaire included more than 200 items and all physicians were trained to carry out the interview, collect information and complete the questionnaire. 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 [16].

Diet information was obtained by a simplified 20-item food frequency questionnaire, based on validated instrument which included standard portions of foods [17-18]. and several response categories: daily consumption, ≥ 3 times / week, 1-2 times / week, <1 time / week, never or almost never. The foods were: dairy products, meats, cold meats and sausages, fish, eggs, legumes, potatoes, vegetables, fruit, rice and pasta, bread, cakes or sweets, olive oil, other oils, animal fat, fried foods, ready meals, preserved food, nuts, bag snacks. Adherence to the Mediterranean diet was estimated through an adaptation of the score used by *Panagiotakos* in the ATTICA study [19]. A score of 0 was 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, Pearson's chi square (categorical variables), p values <0.05 were considered statistically significant. Then it was calculated the percentage of subjects who reverted to normal glycaemia according to these variables and types of prediabetes. Multivariate logistic regression was used to estimate odds ratios (OR) with 95% confidence intervals (CIs) to quantify the association between demographic characteristics, lifestyle variables, obesity, hypertension and biochemical parameters with reversion to normal glycaemia after adjustment for age and sex. ORs of reversion to normal glycaemia associated with type of prediabetes was estimated using three sequential models of adjustment: 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). Confounders were included in each model based on its significant association (p<0.05) or based on established knowledge of acting a risk factor biological mechanism of action (i.e. BMI). Each successive model included the factors from the previous model. Finally, prediabetes was further 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 (group 1), 27.6% had isolated elevated HbA1c levels (group 2) and 50.9% had both altered parameters (group 3). **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; a total of 61% of group 1 population were men, corresponding percentages were 38.9% for group 2 and 50.3% for group 3 , respectively (p<0.001).

Distribution of age was similar within groups, although group 1 tended to be younger. In terms of alcohol consumption, the proportion of daily drinkers were 29% for group 3 compared to 19.5% for group 2 and 34% for group 1. Besides group 3 presented a higher proportion 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 in group 3 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, a total of 7.9% of subjects in group 3 reverted to normal glycaemia, being the lowest proportion compared with 31% for group 1 and 24.4% for group 2, respectively (Figure 1). Additionally, 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 WHO 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. 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

Using as reference group 3 (i.e. participants with both glycemic parameters altered) when adjusting by age and sex, the OR of reversion of prediabetes was 4.87 (95% CI: 3.10-7.65) for group 1 and 3.72 (95% CI: 2.39-5.78) for group 2. 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) and 3.43 (95% CI: 2.17-5.42) (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

Reversion to normal glucose regulation at the third year of follow-up was almost four times higher in subjects with isolated impaired HbA1c and almost five times higher in subjects with isolated impaired FPG, compared with subjects with both altered parameters. Adjustment for lifestyles did not modify markedly the magnitude of association between type of prediabetes and reversion to normoglycemia. Thus, the differences found across groups cannot be explained via lifestyle factors.

Comparison with existing literature

Previous studies evaluating the proportion of reversion to normoglycaemia were heterogeneous in design, duration of follow-up and criteria definition, yielding a broad range of reversion rates [20-24]. Only few did it according to prediabetes criteria [13, 25]. A Japanese study similar to ours observed a greater proportion of reversion rates among those with elevated HbA1c levels [25]. Our results showed an opposite trend resulting in lower rates for individuals with HbA1c levels ≥ 6.0% regardless FPG levels, similar to the results provided by a British study [13]. Using the same prediabetes criteria than ours, other study observed that individuals who reverted to normoglycaemia had a low insulin resistance and optimal beta-cell function at baseline [26]. Therefore, it would be reasonable to think that individuals with HbA1c ≥6% at baseline, had an increased insulin resistance and/or a decreased beta cell function, which might explain the lowest reversion rates found. Although we did not capture fasting plasma insulin, we used other parameters that might serve as a proxy for recognizing insulin resistance. We calculated the triglyceride (TG) glucose (TyG) index and several lipid ratios: TG/HDL ratio, the total TC/HDL ratio, and the LDL/HDL ratio and analysed them in tertile strata. Individuals with HbA1c ≥6% at baseline presented higher levels (Tertile 1) compared with individuals with only impaired FPG. For example, almost 50% of subjects with only impaired FPG were located in tertile 3 while 38.9% of only impaired HBA1c were in tertile 1 and 33% for those with both altered parameters (*data not shown*)

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 studies in subjects with prediabetes that evaluate reversion to normoglycemia through intervention trials focusing on optimal lifestyle actions. The vast majority, although not all [13, 27], draw similar conclusions than ours [4, 20-21, 23-24, 28]. Several trials that compared diet and physical activity promotion programs versus usual care in person with prediabetes reported reversion to normoglycemia between 20% and 52% [29]. Those findings have been confirmed in an intervention trial among persons with high cardiovascular risk [30].

Evidence suggests larger changes in weight with better alignment with lifestyle intervention. Both, obesity and body fat distribution are critical factors to decrease insulin sensitivity and B cells function [31]. And physical activity causes increased glucose uptake into active muscles balanced by hepatic glucose production and it improves insulin action [32]. There is also evidence that Mediterranean diet improves insulin sensitivity and prevents from diabetes [33]. It is probable that individuals reverting to normoglycemia followed an optimal lifestyle behaviour long time before baseline state.

Strengths and limitations

This is the first study evaluating the role of optimal lifestyle factors in the reversion to normoglycemia according type of prediabetes. Our study highlights the feasibility of conducting a prospective study, with data collected nation-wide by primary care physicians during routine clinical practice. Analytical determinations were performed at different laboratories. This fact could result in some source of misclassification. Since each subject was assigned to the same laboratory during the follow-up, this limitation should be minor and non-differential in relation to the outcome, as it is unlikely the relation between the methods employed by specific laboratories and reversion.

A potential source of misclassification when classifying subjects according to FPG levels cannot be ruled out. HbA1c reflects average plasma glucose over the previous eight to 12 weeks [34], while FPG is subjected to daily variation levels [35]. If any substantial impact of misclassification, we would not be able to found the important observed differences to reversion according isolated impaired FPG levels. In addition, this study did not consider participants with prediabetes diagnosed based on oral glucose overload [14]., therefore it was not possible to estimate the prognosis for different categories according to this criterion. Although this is a limitation, in any case its impact would be minor as this measure is rarely used in routine practice

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 [36-37]. The food frequency questionnaire is the most commonly used instrument to assess past dietary intake in epidemiological studies. While the questionnaire of other Spanish study (PREDIMED study) used 14 item food, the PREDAPS Study used 20 in order to include some foods that are eaten as substitutes for the foods that are part of the Mediterranean diet. Therefore, the subjects with high adherence to the Mediterranean diet in the present analysis are strict adherents to this diet, since in the calculation of the score the absence of consumption of these substitute foods has been weighted more. Perhaps this explains that in these subjects the reversion to normoglycemia is 78% higher than in the rest of the subjects. On the other hand, an overestimation of physical activity cannot be excluded due to a possible memory bias of the activities carried out in the last two weeks. However, it is unlikely that this overestimation is differential with respect to the type of prediabetes of the subjects.

Researchers were unable to determine a time-dependent variable. 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. Likewise, we did not include in

the analyses the existence or not of pharmacological treatment, as antihypertensive agents and lipid lowering drugs. In any case, there no was association between pharmacological treatment and reversion to normal glycemia (*data not shown).*

Finally, since reversion to normoglycemia might not be a permanent 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. The subjects who did not reach the third visit were excluded. When evaluating the baseline characteristics of the dropped-out subjects, there were no significant substantial differences with respect to the subjects who remained in the study (Supplement table 1). Therefore, a possible selection bias should be ruled out, it should be minor.

Implications for research and/or practice

The criteria of prediabetes are a controversial topic [38-39]. On the other hand, 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. Since 41% and 33% of the subjects with isolated FPG <110 mg/dl and isolated HbA1c <6% reverted to normoglycemia, respectively, this might lead into an overdiagnosis of prediabetes. Perhaps those subjects would not be the specific target for intensification of optimizing lifestyle factors and other actions such as initiating antidiabetic therapy. Further studies evaluating the role of optimal lifestyles in prognostic results, among subjects with prediabetes classified with different criteria, will be very useful to harmonize definitions on prediabetes and to better identify specific subjects with a low and high probability of normalizing glycaemia levels.

Conclusions

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

Acknowledgements

Ethics approval and consent to participate: 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. Informed consent was obtained from all participants and/or their legal guardians

Consent for publication: Non-applied

Availability of data and materials: Data will be available upon request

Competing interests: None declared

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References

1. NCD Risk Factor Collaboration (NCD-RisC).Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 2016; 387:1513-1530.
2. Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R,Casamitjana R, Castaño L, Castell C, Catalá M, Delgado E, Franch J, Gaztambide S,Girbés J, Gomis R, Gutiérrez G, López-Alba A, Martínez-Larrad MT, Menéndez E, Mora-Peces I, Ortega E, Pascual-Manich G, Rojo-Martínez G, Serrano-Rios M, ValdésS, Vázquez JA, Vendrell J. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. Diabetologia. 2012 Jan;55(1):88-93
3. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS med 2006; 3:e442.
4. Perreault L, Kahn SE, Christophi CA, et al. Diabetes Prevention Program Research Group. Regression from prediabetes to normal glucose regulation in the diabetes prevention program. Diabetes Care

2009;32:1583-1588.

5. Knowler WC, Barrett-Connor E, Fowler SE, et al. Diabetes Prevention Program Research Group Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346:393-403.
6. Meigs JB, Muller DC, Nathan DM, et al. Baltimore Longitudinal Study of Aging. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. Diabetes 2003; 52:1475-1484
7. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. Diabetes Care 2018; 41:S13-S27.
8. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006; 368:1096-1105.
9. Ramachandran A, Snehalatha C, Mary S, et al. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006; 49:289-297.
10. Engberg S, Glümer C, Witte DR, et al. Differential relationship between physical activity and progression to diabetes by glucose tolerance status: the Inter99 Study. Diabetologia 2010; 53:70-78.
11. Færch K, Witte DR, Brunner EJ, et al. Physical activity and improvement of glycemia in prediabetes by different diagnostic criteria. J Clin Endocrinol Metab 2017; 102:3712-3721.
12. Serrano R, García-Soidán FJ, Díaz-Redondo A, et al; Grupo de Estudio PREDADS Cohort Study in Primary Health Care on the Evolution of Patients with Prediabetes (PREDAPS): basis and methodology. Rev Esp Salud Publica 2013; 87:121-135.
13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011; 34:S62–S69.
14. World Health Organization. Global recommendations on physical activity for health. World Health Organization 2010; Geneva
15. Martin-Moreno JM, Boyle P, Gorgojo L, Maisonneuve P, Fernandez-Rodriguez JC, Salvini S, Willett WC. Development and validation of a food frequency questionnaire in Spain. Int J Epidemiol. 1993;22:512–519.
16. Fernández-Ballart JD, Piñol JL, Zazpe I, Corella D, Carrasco P, Toledo E, Perez-Bauer M, Martínez-González MA, Salas-Salvadó J, Martín-Moreno JM. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. Br J Nutr. 2010;103:1808–1816
17. Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. Nutr Metab Cardiovasc Dis 2006; 16:559-568

18. Wong MS, Gu K, Heng D, et al. The Singapore impaired glucose tolerance follow-up study: does the ticking clock go backward as well as forward?. Diabetes Care 2003; 26:3024-3030.
19. Janghorbani M, Amini M. Normalization of glucose intolerance in first-degree relatives of patients with type 2 diabetes. Diabetes Res Clin Pract 2010; 88:295-301.
20. Tabák AG, Herder C, Rathmann W, et al. Prediabetes: a high-risk state for diabetes development. Lancet 2012; 379:2279-2290.
21. Perreault L, Pan Q, Mather KJ, et al. Diabetes Prevention Program Research Group. Effect of regression from prediabetes to normal glucose regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study. Lancet 2012; 379:2243-2251.
22. Guo VY, Yu EY, Wong CKh, et al. Validation of a nomogram for predicting regression from impaired fasting glucose to normoglycaemia to facilitate clinical decision making. Fam Pract 2016; 33:401-407.
23. Heianza Y, Arase Y, Fujihara K, et al. Screening for pre-diabetes to predict future diabetes using various cut-off points for HbA(1c) and impaired fasting glucose: the Toranomon Hospital Health Management Center Study 4 (TOPICS 4). Diabet Med 2012; 29:e279-e285.
24. Kim CH, Kim HK, Kim EH, et al. Longitudinal changes in insulin resistance, beta-cell function and glucose regulation status in prediabetes. Am J Med Sci 2018; 355:54-60.
25. Kowall B, Rathmann W, Heier M, et al. Impact of weight and weight change on normalization of prediabetes and on persistence of normal glucose tolerance in an older population: the KORA S4/F4 study. Int J Obes (Lond) 2012; 36:826-833.
26. Alvarsson M, Hilding A, Ostenson CG. Factors determining normalization of glucose intolerance in middle-aged Swedish men and women: a 8-10-year follow-up. Diabet Med 2009; 26:345-353.
27. Balk EM, Earley A, Raman G, Avendano EA, Pittas AG, Remington PL. Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. Ann Intern Med. 2015;163(6):437–451. doi:10.7326/M15-0452
28. Salas-Salvadó J, Bulló M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N,Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Romaguera D, Lapetra J,Lamuela-Raventós RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV,Martínez-González MA. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. Ann Intern Med. 2014 Jan 7;160(1):1-10
29. Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. Diabetes Metab Syndr Obes 2014; 7:587-591
30. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016; 39:2065-2079
31. Kirpitch AR, Maryniuk MD. The 3 R's of glycemic index: recommendations, research, and the real world. Clinical Diabetes 2011; 29:155-159
32. World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. World Health Organization 2011; Geneva

33. Mooy JM, Grootenhuis PA, de Vries H, et al. Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn Study. Diabetologia 1996; 39:298-305
34. Grandjean AC. Dietary intake data collection: challenges and limitations. Nutr Rev. 2012;70(Suppl 2):S101–4
35. Willett W. Nutritional epidemiology. In: Rothman KJ, Greenlands S. Modern Epidemiology. Philadelphia: Lippincott Williams & Wilkins, 1998: 623-642

Tables

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

Characteristics	Group 1* Isolated impaired FPG		Group 2f Isolated elevated HbA1c		Group 3y Both altered parameters		*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	251	55.2	112	112	112	52.0			

recommendations									
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

* Group 1, Isolated impaired FPG. Defined as FPG:100-125 mg/dl and HbA1c: <39 mmol/mol (<5.7%)

f Group 2 Isolated elevated HbA1c. Defined as FPG: <100 mg/dl and HbA1c:39-47 mmol/mol (5.7-6.4%)

y Group 3 Both altered parameters. Defined as FPG:100-125 mg/dl and HbA1c:39-47 mmol/mol (5.7-6.4%)

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

Characteristics, N=948	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				
Group 3, Both altered parameters	1,00	1,00	1,00	1,00
Group 2, Isolated elevated HbA1c	3.72 (2.39-5.78)	3.59 (2.30-5.60)	3.43 (2.17-5.42)	3.09 (1.92-4.97)
Group1, Isolated FPG	4.87 (3.10-7.65)	4.78 (3.03-7.55)	4.52 (2.84-7.18)	4.55(2.84-7.28)
Prediabetes subtype				
HbA1C ≥42 mmol/mol(≥6%) and FPG 100–125 mg/dl	1,00	1,00	1,00	1,00
HbA1c<42 mmol/mol (<6%) and FPG 100–125 mg/dl	4.54 (2.03-10.17)	4.46 (1.99-9.99)	4.36 (1.94-9.80)	4.47 (1.98-10.06)
Isolated HbA1c≥42 mmol/mol (≥6%)	2.81 (1.02-7.74)	2.75 (0.99-7.61)	2.70 (0.97-7.51)	2.43 (0.84-7.05)
Isolated HbA1c <42 mmol/mol (<6%)	14.65 (6.73-31.91)	14.11 (6.44-30.94)	13.34 (6.03-29.52)	11.84 (5.30-26.46)
Isolated FPG≥110 mg/dl	6.18 (2.50-15.30)	6.03 (2.43-14.98)	5.75 (2.30-14.37)	5.99 (2.38-15.13)
Isolated FPG<110 mg/dl	19.76 (8.84-44.15)	19.28 (8.60-43.25)	18.21 (8.08-41.06)	18.47 (8.14-41.90)

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 variable

Model D: Model A plus alcohol consumption, smoking, BMI, abdominal obesity, physical activity, adherence to Mediterranean diet plus hypertension and all the ratios

Figures

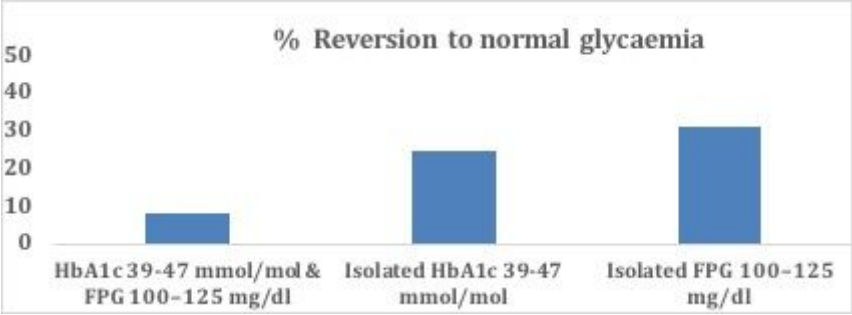

Figure 1

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

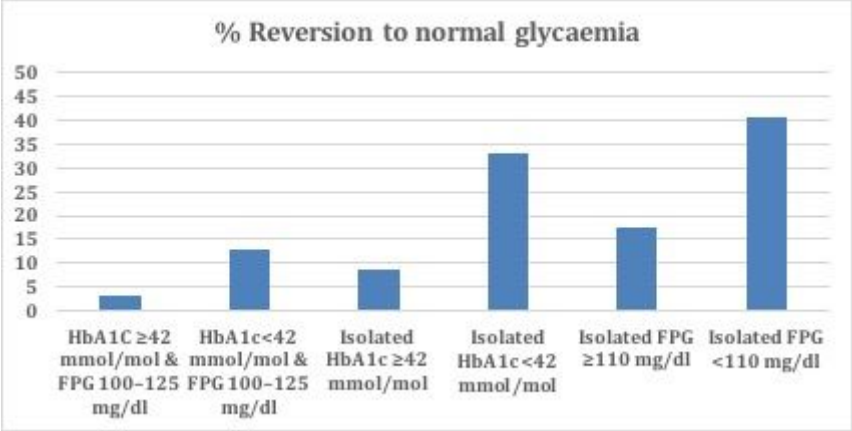

Figure 2

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

Supplementary Files

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