

Clinical and metabolic predictors of regression to normoglycemia in a population at intermediate cardiometabolic risk

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Original investigation

Keywords: dysglycemia, regression to normoglycemia, metabolomics, cardiometabolic risk

Posted Date: November 18th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-109666/v1>

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Version of Record: A version of this preprint was published on February 27th, 2021. See the published version at <https://doi.org/10.1186/s12933-021-01246-1>.

Abstract

Background: Impaired fasting glucose (IFG) is a prevalent and potentially reversible intermediate stage leading to type 2 diabetes that increases risk for cardiometabolic complications. The identification of clinical and molecular factors associated with the reversal, or regression, from IFG to a normoglycemia state would enable more efficient cardiovascular risk reduction strategies. The aim of this study was to identify clinical and biological predictors of regression to normoglycemia in a non-European population that is characterized by increased type 2 diabetes conversion rates.

Methods: We conducted a prospective, population-based study among 9,637 Mexican individuals using clinical features and plasma metabolites. Among them, 491 subjects were classified as IFG, defined as fasting glucose between 100 and 125 mg/dL. Regression to normoglycemia was defined by fasting glucose less than 100 mg/dL in the follow-up visit. Plasma metabolites were profiled by Nuclear Magnetic Resonance. Multivariable Cox regression models were used to examine the associations of clinical and metabolomic factors with regression to normoglycemia. We assessed the predictive capabilities to regress to normoglycemia of models that included clinical factors alone and models that included clinical factors and prioritized metabolites.

Results: During a median follow-up period of 2.5 years, 22.6% of participants (n=111) regressed to normoglycemia, and 29.5% progressed to type 2 diabetes (n=145). The multivariate adjusted relative risk of regression to normoglycemia was 1.10 (95% confidence interval [CI], 1.25 to 1.32) per 10 years of age increase, 0.94 (95% CI, 0.91-0.98) per 1 SD increase in BMI, and 0.91 (95% CI, 0.88 – 0.95) per 1 SD increase in fasting glucose. A model including information from age, fasting glucose, and BMI showed a good prediction of regression to normoglycemia (AUC = 0.73 (95% CI, 0.66 - 0.78)). Adding information from prioritized metabolites (TG in large HDL, albumin, and citrate) marginally improved the predictive capability beyond clinical factors (AUC = 0.74 (95% CI 0.68 - 0.80), p value = 0.485)

Conclusion: In individuals with IFG, information from three clinical variables easily obtained in the clinical setting showed a good prediction of regression to normoglycemia beyond metabolomic features. Our findings can serve to inform and design future cardiovascular prevention strategies.

Background

Impaired fasting glucose, a highly prevalent intermediate stage between normal glucose tolerance (NGT) and type 2 diabetes (T2D) (1), is characterized by metabolic alterations that lead to increased type 2 diabetes and cardiovascular complications (2,3). Empirical evidence support that individuals with type 2 diabetes are at 2-fold increased cardiovascular risk as compared to people without type 2 diabetes (4,5), indication that preventing new onset of type 2 diabetes is an efficient approach to reduce cardiovascular burden. A number of studies have demonstrated the effectiveness of controlling cardiovascular risk factors to reduce the risk of cardiovascular outcomes among patients with diabetes and prediabetes (6–12). The identification of clinical and molecular features associated with regression to normoglycemia has the potential to inform the design and implementation of more efficient cardiovascular risk-reduction strategies.

Preliminary evidence from prospective epidemiological studies have identified clinical predictors of regression to normoglycemia including age (13,14), baseline fasting glucose (13–18), absence of postprandial hyperglycemia (13), higher insulin secretion (13,17), lower BMI (17), preserved β -cell function (17,18), lower fasting triglycerides (16,17), and higher baseline muscle mass (16). These studies have been mainly conducted in individuals from European or Asian ancestry, and the extent to which previous findings are similar in other populations with rapid conversion rate from impaired fasting glucose to type 2 diabetes such as Latino populations is unknown. In addition to clinical factors, the use of metabolomics data could provide valuable information to identify individuals who are more likely to regress to normoglycemia in order to develop more tailored interventions. Here, we analyzed longitudinal data from 9,637 participants free of diabetes at baseline from the Mexican Study on Nutritional and Psychosocial Markers of Frailty (19) to

identify clinical and biological predictors of regression to normoglycemia and establish whether adding information from plasma metabolites could improve the predictive capability for regression to normoglycemia beyond clinical factors.

Materials And Methods

Study design and populations

We used data from a prospective observational cohort study of Mexican adults living in large urban settings of central Mexico. The study sample was comprised of healthy adults ≥ 20 years old, with body mass index (BMI) ≥ 20 kg/m², without previously diagnosed diabetes, cardiovascular disease, and cerebral vascular disease. Exclusion criteria included pregnancy; alcohol habit defined as consuming more than 10 servings of alcohol per week. Potential participants were evaluated at their workplaces (offices of the federal government or private companies), homes or during a visit of a relative to a medical unit. In the baseline visit, was recorded the personal medical history, family history of type 2 diabetes, years of formal education, and socioeconomic status. The cohort is composed by 9,637 participants with baseline evaluation, the follow-up examinations took place after a three-year period (± 6 months). The response rate was 63.7% (N = 6144) subjects had follow-up information. Impaired fasting glucose (IFG) was defined according to the American Diabetes Association guidelines of fasting plasma glucose between 100 and 125 mg/dL (20) and the analysis sample was restricted to the IFG subset of the cohort.

The study was approved by the Ethics Committee of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Written informed consent was obtained from each participant. Investigation was conducted in accordance with the Helsinki Declaration of Human Studies principles.

Assessment of regression to normoglycemia

Regression to normoglycemia was defined as one measurement of fasting glucose < 100 mg/dL in subsequent visit among individuals who were not taking glucose lowering medication including insulin. Incident type 2 diabetes was defined according to the World Health Organization criteria, including fasting plasma glucose ≥ 126 mg/dL, report of taking any glucose lowering medication including insulin or diagnosis of type 2 diabetes by a health professional.

Assessment of clinical factors

Anthropometric measurements were conducted following standardized protocols. Subjects were evaluated in fasting, with light clothing and without shoes. Weight and height were used to compute BMI, as the ratio of weight (kilograms nearest 0.01) to squared height (m²). Waist and hip circumference (centimeters nearest 0.5) were measured at the midpoint between the lower ribs and the iliac crest, and at the level of the trochanter major respectively. Both were used to calculate the waist-hip index. Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) was calculated using the following formula: fasting glucose (mg/dL) * fasting insulin / 405 (21). Homeostasis Model Assessment for cell-beta function (HOMA-B) was estimated with the following formula: $20 * \text{fasting insulin (mmol/L)} - 3.5$ (21). Insulin sensitivity was estimated also using METS-IR; it was computed as $\text{Ln}((2 * \text{fasting glucose (mg/dL)}) + \text{fasting triglycerides (mg/dL)}) * \text{Body Mass Index (BMI)} / (\text{Ln(HDL-c)})$ (22). Physical activity (physically active vs sedentary habit) was measured using the International Physical Activity Questionnaire (23). Sedentary behavior is defined as any seated or reclined posture (e.g. sitting, lying down, and driving) that expends 1.50 or less Metabolic Equivalent Tasks (METs) while moderate to vigorous physical activity (MVPA) is any activity that expends 3.00 or more METs. Hypertension was defined as a systolic blood pressure (SBP) of ≥ 140 mm Hg, or a diastolic blood pressure (DBP) of ≥ 90 mm Hg, or taking antihypertensive medication, or self-report of previous diagnosis. Fasting triglycerides concentrations > 150 mg/dL were classified as hypertriglyceridemia. Obesity was defined BMI > 30 kg/m², and abdominal obesity was classified according Adult Treatment Panel III (24), waist circumference > 102 cm in males and > 88 cm in females.

All serum samples kept frozen until processed in a central laboratory certified by the External Comparative Evaluation of Laboratories Program of the College of American Pathologists (Departamento de Endocrinología y Metabolismo, Instituto Nacional de Ciencias Médicas y Nutrición, México City). Blood samples were drawn from the radial vein after ~ 9 hours fasting and were placed in EDTA-treated tubes (BD-vacutainer TM, London, UK). Samples were centrifuged for 15 min at 3000 rpm at 4°C and stored at -80°C until the analysis. Serum concentration of glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-c), were analyzed as was described previously (19).

Metabolite determinations

Metabolites were analyzed by proton Nuclear Magnetic Resonance (NRM) in serum samples. The methodology has been previously described in detail (25). In brief, the procedure defines three molecular windows to obtain information on a) lipoprotein subclasses including chylomicrons or large VLDL particles), b) serum lipid components including ω -3 and ω -6, poly, mono, and saturated fatty acids, phospholipids (PL), triglycerides (TG), cholesterol (C), free cholesterol (FC), and cholesterol esters (CE), apolipoprotein A-I and APOB, and c) low molecular weight components including alanine, glutamine, glycine histidine, isoleucine, leucine, valine, phenylalanine, tyrosine, acetate, acetoacetate, 3-hydroxybutyrate, creatinine, albumin and glycoprotein acetyl (a-1 acid glycoprotein). Quality control procedures were performed according a previous metabolomics pipeline including the following steps: (1) remove metabolites with > 25% missing data, (2) log-transform the remaining metabolites, and (3) perform rank-based inverse normal transformation to calculate metabolite abundance z-scores.

Statistical analysis

The study sample was categorized into three groups according to glycemic status at the end of follow-up: regression to normoglycemia, impaired fasting glucose maintenance, or progression to type 2 diabetes. Comparisons between these three groups were tested with one-way ANOVA for continuous variables or with chi-square test for qualitative variables. Clinical categorical variables were reported as frequencies and percentages. Quantitative variables were reported as means and standard deviation for normal distributed variables or median and interquartile range for non-normal distributed variables.

We used multivariable Cox proportional hazards models to calculate hazard ratios (HR), and 95% confidence interval (95% CI) for regression to normoglycemia for clinical and metabolomic factors. Variables with evidence of nominal significant association in the bivariate analysis, that did not exhibit collinearity (variance inflation factor > 7), were selected for inclusion in predictive models. The best model was selected as the set of variables with the highest discriminatory capability according to the C statistic and the area under the receiver operating characteristic curve (ROC). To correct overfitting in the AUC, we used 2000 stratified bootstrap replicates with 95% confidence intervals. The difference between the predictive capability between estimates from the clinical and clinical + metabolomic models was tested with the DeLong test (26). Sensitivity analyses were conducted to investigate associations with HOMA-IR and HOMA-B using linear regression modeling accounting for, follow-up time, confounders, and corresponding baseline values. We considered two sided α level of 0.05 for all analyses.

All analyses were conducted using R software version 3.4.3.

Results

From 9,637 participants included in the primary cohort, a total of 491 individuals were eligible for this analysis based on their impaired fasting glucose status at baseline. The most frequent cause of exclusion from the primary cohort was glycemia < 100 mg/dL at baseline, which excluded 56.43% participants (N = 2,808). After ~ 2.5 years of follow-up, n = 111(22.6% of N = 491) participants regressed to normoglycemia, while 235 (47.9%) remained as impaired fasting glucose and 145 (29.5%) progressed to type 2 diabetes. Baseline characteristics from included participants according to glycemic phenotypes at the end of follow-up are shown in Table 1. Compared with individuals who progressed to type 2 diabetes or

maintained their impaired fasting glucose status, individuals who regressed to normoglycemia had lower fasting glucose concentrations ($p < 0.001$), and lower BMI ($p = 0.049$).

Table 1
Baseline characteristics between groups according final glucose status (n = 491)

	Overall (n = 491)	Regression to normoglycemia (n = 111)	IFG Maintenance (n = 235)	Progressed to T2D (n = 145)	<i>p</i> value
Age (years)	48.72 ± 11.02	49.98 ± 11.2	48.35 ± 11.00	48.34 ± 10.87	0.27
Women n, (%)	327, (66.59)	75, (67.5)	161, (68.5)	91 (62.7)	0.498
Hypertension	341 (69.45)	76, (68.4)	173, (73.6)	92, (63.4)	0.262
Years of education	11.72 ± 5.01	12.52 ± 5.41	11.61 ± 4.99	11.29 ± 4.68	0.061
BMI (kg/m ²)	30.15 [6.3]	29.45[6.4]	30.00 [5.5]	30.78 [7.25]	0.049*
Obesity n, (%)	248 (50.5)	51(45.9)	116 (49.36)	81(55.86)	0.258
Abdominal obesity n, (%)	298 (60.6)	58(52.2)	144(61.27)	96(66.2)	0.074
Sedentary habit n, (%)	348 (70.8)	76, (68.4)	169, (72)	103, (71)	0.804
Fasting glucose (mg/dL)	105.00 [8]	103.00 [6]	105.00 [8]	108.00 [12]	0.001*
Fasting insulin (UI)	14.80 [11.2]	13.80 [11.05]	15.05 [10.2]	14.6 [11.5]	0.508
HOMA-IR	3.92 [2.9]	3.6 [2.9]	4.0 [2.7]	3.95 [3.28]	0.285
HOMA-B	46.83 [37.23]	44.50 [39.91]	47.41 [34.6]	46.02 [38.67]	0.673
METS-IR	49.40 [12.11]	48.45 [13]	49.44 [11.3]	50.48 [12.2]	0.289
Triglycerides (mg/dL)	197.00 [121]	200.00 [169]	188.00 [112]	205.00 [116]	0.542
Hypertriglyceridemia n, (%)	355 (72.3)	76 (68.4)	169 (71.9)	110 (75.86)	0.417
Total-Cholesterol (mg/dL)	217.42 ± 42.70	224.69 ± 45.3	214.39 ± 43.	216.76 + 39.44	0.184
HDL-c (mg/dL)	42.14 ± 10.65	43.05 ± 10.11	41.29 ± 10.10	42.82 ± 11.84	0.987
LDL-c (mg/dL)	134.51 ± 32.74	138.78 ± 31.0	133.77 ± 35.04	132.60 + 29.83	0.232
Apolipoprotein-B (mg/dL)	116.00 [38.4]	120.0 [36.5]	115.00 [39.35]	115.00 [37]	0.712

Overall (n = 491)	Regression to normoglycemia (n = 111)	IFG Maintenance (n = 235)	Progressed to T2D (n = 145)	<i>p</i> <i>value</i>
<p>ATP III.- Adult treatment panel III. Abdominal Obesity Male > 102 cm Female > 88 cm. Hypertension: >130 mmHg or > 88 mmHg or taking antihypertensive medication, or self-report of previous diagnosis. BMI: Body Mass Index (Kilogram/Height²). HOMA-IR: Homeostasis Model Assessment for Insulin Resistance (Fasting glucose* Fasting Insulin /405), Hypertriglyceridemia: Fasting triglycerides > 150 mg/dL</p> <p>HDL-C: High-density lipoprotein cholesterol. LDL-c Low-density lipoprotein-cholesterol. One-way ANOVA was used to compute the <i>p value</i> between three groups. IFG: Impaired Fasting glucose IFG. T2D. Type 2 Diabetes</p>				

Clinical variables associated with regression to normoglycemia

The multivariable-adjusted Hazard ratio (HR) of regression to normoglycemia was 1.10 (95% confidence interval [CI] 1-1.03) per 10 years of age, 0.94 (95% CI = 0.91–0.98) per 1 standard deviation (SD) increase in BMI, 0.91 (95% CI = 0.88–0.95) per 1 SD increase in fasting glucose, 0.91 (95% CI = 0.84 to 0.99) per 1SD increase in HOMA-IR, and 0.99 (95% CI = 0.94–0.98) per 1 SD increase in METS-IR (Table 2).

Table 2

Cox proportional hazard model regression results of clinical factors associated with regression to normoglycemia

	HR	CI 95%	<i>p value</i>
Age (10 years)	1.019	1.10–1.30	0.044
Sex	0.779	0.52–1.16	0.226
Hypertension	0.819	0.54–1.23	0.341
Years of education	0.994	0.95–1.03	0.771
BMI (kg/m ²)	0.947	0.91–0.98	0.009
Obesity n, (%)	0.630	0.43–0.92	0.017
Abdominal obesity n, (%)	0.586	0.40–0.85 -	0.006
Sedentary habit n, (%)	0.768	0.51–1.15	0.206
Fasting glucose (mg/dL)	0.919	0.883–0.956	0.001
Fasting insulin (UI)	0.980	0.95–1.002	0.070
HOMA-IR	0.916	0.845–0.99	0.03
HOMA-B	0.995	0.98–1.02	0.139
METS-IR	0.996	0.94–0.98	0.002
Triglycerides (mg/dL)	0.99	0.99–1.00	0.863
Hypertriglyceridemia n, (%)	0.75	0.50–1.12	0.168
Total-Cholesterol (mg/dL)	1.002	0.99 -1.00	0.259
HDL-c (mg/dL)	1.01	0.99–1.02	0.169
LDL-c (mg/dL)	1.04	0.99–1.01	0.271
Apolipoprotein-B (mg/dL)	1.01	0.99–1.08	0.742
BMI: Body Mass Index. <i>p value</i> was computed in a Cox regression model comparing subjects who regress to normoglycemia and subjects to progressed to type 2 diabetes (T2D)			

Metabolomic variables associated with regression to normoglycemia

After adjustment for potential confounders, we identified 18 metabolites associated with regression to normoglycemia in models adjusting for baseline age, sex, BMI, and fasting glucose (Fig. 1). Ten metabolites showed a positive association with regression to normoglycemia, most of them capturing different HDL composition characteristics (Hazard Ratios [HR] ranging from 1.22 to 1.32 per 1 SD increment). Eight metabolites showed a negative association with regression to normoglycemia, including three LDL composition-related and two VLDL composition-related (HR ranging from 0.72 to 0.80 per 1 SD increment).

The multivariable adjusted relative risk of regression to normoglycemia was 1.32 (95% CI 1.09–1.61) per 1 SD-increment in cholesterol esters in very large HDL, 1.31(95% CI 1.07–1.59) per 1 SD-increment in total lipids in very large HDL, 1.30, (95% CI 1.07–1.59) per 1 SD-increment concentration of large HDL particles, 1.29 (95% CI 1.06–1.57) per 1 SD-increment in total cholesterol in very large HDL, and 0.73 (95% CI 0.59–0.90) per 1 SD-increment in albumin. In addition, we showed that some metabolites featuring LDLc composition lipoproteins were inversely associated with regression to

normoglycemia including phospholipids in medium LDL, 0.78 (95% CI 0.63–0.96), free cholesterol in small LDL 0.79 (95% CI 0.64–0.98), phospholipids in large LDL, 0.79 (95% CI 0.64–0.98). In a sensitive analysis, we identified twenty-five metabolites associated with HOMA-IR and/or HOMA-B levels (Table 3).

Table 3
Metabolites at baseline associated with HOMA-IR and HOMA-B in the follow-up

Metabolites	Metabolites associated with HOMA-IR				Metabolites associated with HOMA-B			
	β	SE	CI 95%	<i>p</i> value	β	SE	CI 95%	<i>p</i> value
Phospholipids in large HDL	-0.14	0.04	-0.24 - -0.04	0.003	-0.11	0.04	-0.20 - -0.02	0.011
Concentration of large HDL particles	-0.15	0.04	-0.24 - -0.05	0.002	-0.11	0.04	-0.20 - -0.02	0.012
Total lipids in very large HDL	-0.15	0.04	-0.24 - -0.05	0.002	-0.12	0.10	-0.20 - -0.02	0.008
Creatinine	0.10	0.04	0.005-0.20	0.038	0.12	0.04	0.03-0.21	0.009
Mean diameter for HDL particles	-0.12	0.04	-0.22 - -0.03	0.007	-0.10	0.04	-0.19 - -0.01	0.021
Free cholesterol in large HDL	-0.13	0.05	-0.23 - -0.03	0.008	-0.11	0.04	-0.21 - -0.02	0.012
Cholesterol esters in very large HDL	0.09	0.04	0.001-0.19	0.04				
Free cholesterol in very large HDL	-0.15	0.04	-0.24 - -0.05	0.001	-0.11	0.04	-0.20 - -0.02	0.012
Total cholesterol in large HDL	-0.13	0.05	-0.23 - -0.03	0.008	-0.12	0.04	-0.21 - -0.09	0.010
Cholesterol esters in large HDL	-0.13	0.05	-0.23 - -0.03	0.008	-0.12	0.04	-0.21 - -0.03	
Total lipids in large HDL	-0.12	0.05	-0.22 - -0.03	0.010	-0.12	0.04	-0.21 - -0.02	0.010
Concentration of large HDL particles	-0.12	0.05	-0.22 - -0.03	0.010	-0.12	0.04	-0.21 - -0.02	0.010
Phospholipids in medium HDL	-0.13	0.05	-0.22 - -0.03	0.009	-0.12	0.04	-0.21 - -0.03	0.009
Total cholesterol in very large HDL	-0.12	0.04	-0.21 - -0.02	0.014	-	-		-
Total cholesterol in HDL2	-0.11	0.04	-0.21 - -0.02	0.016	-0.09	0.04	-0.18 - -0.009	0.03
Total cholesterol in HDL	-0.10	0.04	-0.20 - -0.01	0.02	-0.09	0.04	-0.18 - -0.002	0.04
Free cholesterol in medium HDL	-0.10	0.04	-0.20 - -0.009	0.03	-	-		-
Cholesterol esters in very large HDL	-0.10	0.04	-0.20 - -0.009	0.03	-	-		-
Mean diameter for LDL particles	0.10	0.04	0.009-0.20	0.03	0.010	0.04	0.01-0.19	0.021
Free cholesterol in very large HDL	-0.10	0.04	-0.19 - -0.005	0.03	-	-		-
Cholesterol esters in small VLDL	0.10	0.04	0.005-0.20	0.03	-	-		-
Total cholesterol in small VLDL	0.10	0.04	0.004-0.20	0.04	-	-		-

	Metabolites associated with HOMA-IR				Metabolites associated with HOMA-B			
Triglycerides in medium HDL	0.10	0.04	0.002–0.19	0.04				
Triglycerides in small VLDL					-0.09	0.04	-0.18 - -0.001	0.04
Triglycerides in medium HDL					-0.10	0.04	-0.19 - -0.01	0.02
p values were computed with a linear regression model considering as confounders: age, sex, body mass index, and baseline values: HOMA-IR and HOMA-B respectively. Bold metabolites represent those associated with normal fasting glucose regression. CI: 95% Interval Confidence. SE: Standard error.								

Predictors of regression to normoglycemia

The clinical variables with higher performance to predict regression to normoglycemia were age, fasting glucose, and BMI (AUC = 0.727, 95% CI 0.66–0.78). We next investigated whether adding uncorrelated metabolomic features to the clinical prediction model improved the predictive capability of the model. We showed that adding information from triglycerides in large HDL, albumin, citrate, increased the AUC to 0.744 but the difference with the clinical prediction model was not significant (95% CI = 0.68–0.80; $p = 0.485$; Fig. 3).

Discussion

Here, we inform the regression and progression rates of dysglycemia in a set of adults with impaired fasting glucose living in urban centers of Central Mexico. After ~ 2.5 years of follow-up, 22.6% subjects regressed to normoglycemia, 36% remained as impaired fasting glucose and 22.9% progressed to type 2 diabetes. We showed that age, lower BMI, and lower glycemia were the main clinical predictors associated with regression to normoglycemia, and that the addition of metabolomics information did not materially improved the predictive capability of a model that included clinical variables alone. Taken together, our findings may have implications for cardiovascular prevention strategies as they identify a set of clinical features that are associated with less likelihood for developing type 2 diabetes among individuals with impaired fasting glucose.

To our knowledge, this is the first report of the rate of regression in Latin-American populations, a population that is characterized by the high conversation rates from impaired fasting glucose to type 2 diabetes. There are few studies that have focused on regression to normoglycemia despite it is the most common and profitable outcome in the midterm and long-term respectively. Our results allow us to compare the regression rates in Mexicans compared against other populations. The rate found in this study is higher to what was found in an Asian and in a multiethnic cohort at 1 and 10 years of follow-up (15,27). Our findings concurs with data from the Diabetes Prevention Program (DPP) showing that within treatment groups, normoglycemia was attained once in 23% (170/736), 25% (161/647) and 23% (137/607), in intensive life style, metformin, and placebo treatment arms, respectively (17). Our findings reinforce the identification of individuals with impaired fasting glucose to advance the prevention of type 2 diabetes, to overcome the burden of cardiometabolic complications. The identification of the variables that predict a higher likelihood for having regression may be useful to prioritize access to care, particularly in populations where the medical access is limited. Our findings confirm the importance of fasting glucose and BMI in the profile of the subjects who achieve regression to normoglycemia and expand them to age, which has been shown very relevant for maintaining normal glucose levels (28) (29).

A novel contribution of our study is that we investigated the associations of circulating metabolites with regression to normoglycemia. In this study we identified 18 associated with regression to normoglycemia. Metabolites associated with regression to normoglycemia highlight features of lipid content in specific lipoprotein subfractions. We showed that the

amount of phospholipids in medium or large LDL particles of free cholesterol in small LDL was associated with lower likelihood to regress to normoglycemia, while lipid components in large HDLc particles were associated with increased likelihood to regress to normoglycemia.

Although, there is lack of information regarding the clinical implications and usability of HDL particles, some evidence describes a negative relationship between the number of large HDL particles and cardiovascular disease, and conversely, a reduced mean HDL size is equally associated with cardiovascular disease in large-scale clinical studies(33). This direction of the effect was confirmed by our study in the associations with insulin sensitivity and secretion where larger HDL particles had a negative association with insulin sensitivity in subject who remained as impaired fasting glucose or regressed to normoglycemia. Our findings support evidence of the clinical usability of a detailed lipid metabolomic profiling and their clinical consequences. Although further studies are needed, HDL composition profile can be used as biomarkers of cardiovascular deterioration even in an early state such as impaired fasting glucose. However, prioritized metabolites marginally improved the predictive capability to regress to normoglycemia suggesting that metabolomic contributions in regression to normoglycemia are more related to the identification of metabolic pathways over prediction.

In our study we found that individuals with low concentrations of albumin at baseline were more likely to regress to normoglycemia, even adjusting for age, BMI and fasting glucose concentrations ($p < 0.003$). Serum albumin is the main protein of the plasma, its main function is the regulation of the colloidal osmotic pressure of the blood (30). Previous reports show inverse associations with type 2 diabetes-related traits (31)(32). Some differences might lie in the studied sample size, most of studies have been studied the risk of healthy individuals to develop type 2 diabetes, whereas our sample is composed by high-risk subjects with impaired fasting glucose. Therefore, the protective capability conferred by the albumin thought its role as antioxidant might be diminished.

There are several limitations in our study including the use of only one measurement of fasting glucose measurement to define regression to normoglycemia. This limits to identify the inter-individual variability of fasting glucose measurements but has the advantage to reduce costs and possible withdrawals that of future visits imply. Our finding need to be confirmed in an independent cohort and other populations at high risk of type 2 diabetes, with longer follow-up times. We acknowledge that this sample is composed only for Latino subjects, further studies in other high-risk populations are need it. Finally, additional studies to test the treatment response will complement the evidence in regards the usability of these variables.

Conclusions

The findings from this study provide quantitative evidence on the progression and regression rates of dysglycemia and identify a set of clinical features that are associated with regression to normoglycemia among individuals with impaired fasting glucose. We also provide evidence about the role of specific lipoproteins subtypes on the regression to normoglycemia and highlight the role of HDL and LDL particles composition. Yet, we showed that the addition of metabolomics information did not improve the capability to predict regression to normoglycemia. Our findings can serve to inform and design future strategies to advance the prevention to type 2 diabetes and related cardiometabolic complications

List Of Abbreviations

BMI: Body Mass Index

IFG: Impaired fasting glucose

HDL: High density lipoprotein

LDL: Low density lipoprotein

VLDL: Very low-density lipoprotein

METs: Metabolic Equivalent Tasks

HOMA: Homeostasis model assessment

NMR: Nuclear magnetic resonance

AUC: Area under the curve

HR: Hazard Ratio

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Written informed consent was obtained from each participant.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The project was supported by a grant from the “Consejo Nacional de Ciencia y Tecnología (CONACyT)” (S0008–2009–1-115250) and research grant by 526 Sanofi. J.M. was partially supported by the European Commission Horizon 2020 program (H2020-MSCA-IF-2015-703787) and by the National Institutes of Health (P30 DK40561). The funding bodies had no roles in the design of the study and collection, analysis, interpretation of data and in writing the manuscript.

Authors' contributions

MRS.G. Analysis and interpretation of the data. Wrote the manuscript. J.M. Reviewed and edited the manuscript. H.M.M. Reviewed and edited the manuscript. R.R.M. Reviewed and edited the manuscript. D.V.G.V. Researched the data. A.K.M. Analysis and interpretation of the data. Reviewed and edited the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors express their gratitude to the study subjects and the investigators that have made significant contributions to the work from the Department of Endocrinology and Metabolism (Luz Elizabeth Guillen Pineda and Carmen Moreno) of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

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Figures

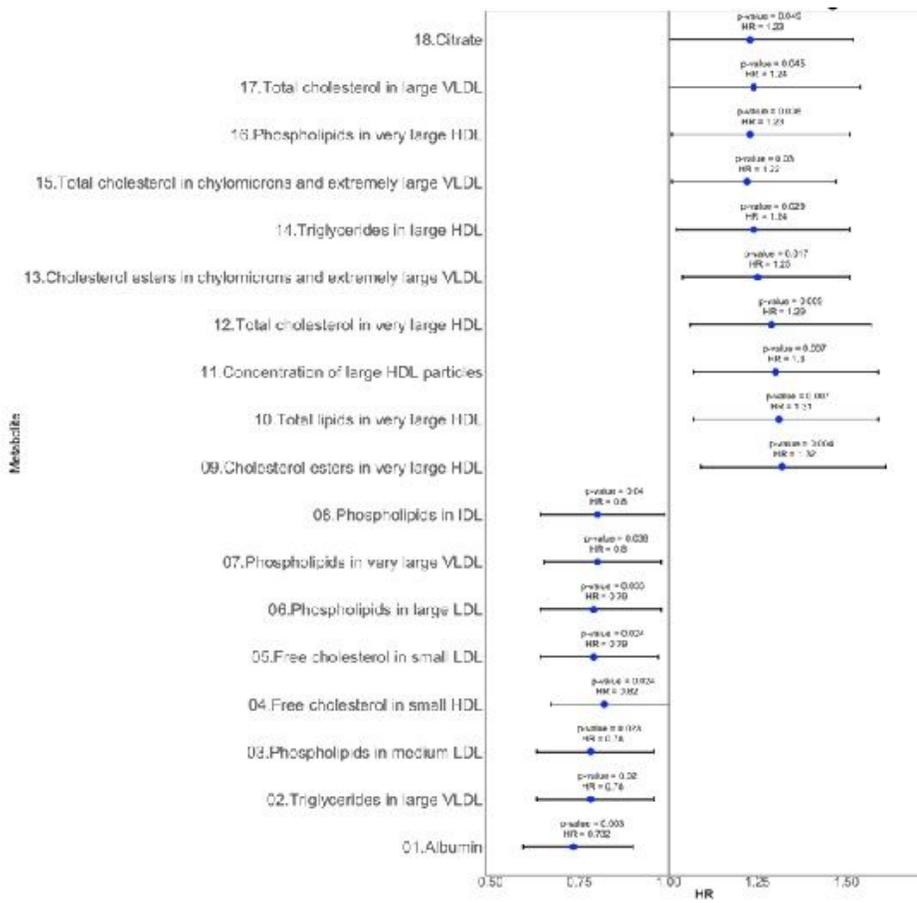


Figure 1

Metabolites associated with regression to normoglycemia ($p < 0.05$). HR: Hazard Ratio and their CI 95%, models were adjusted by baseline variables: age, sex, body mass index, and fasting glucose.

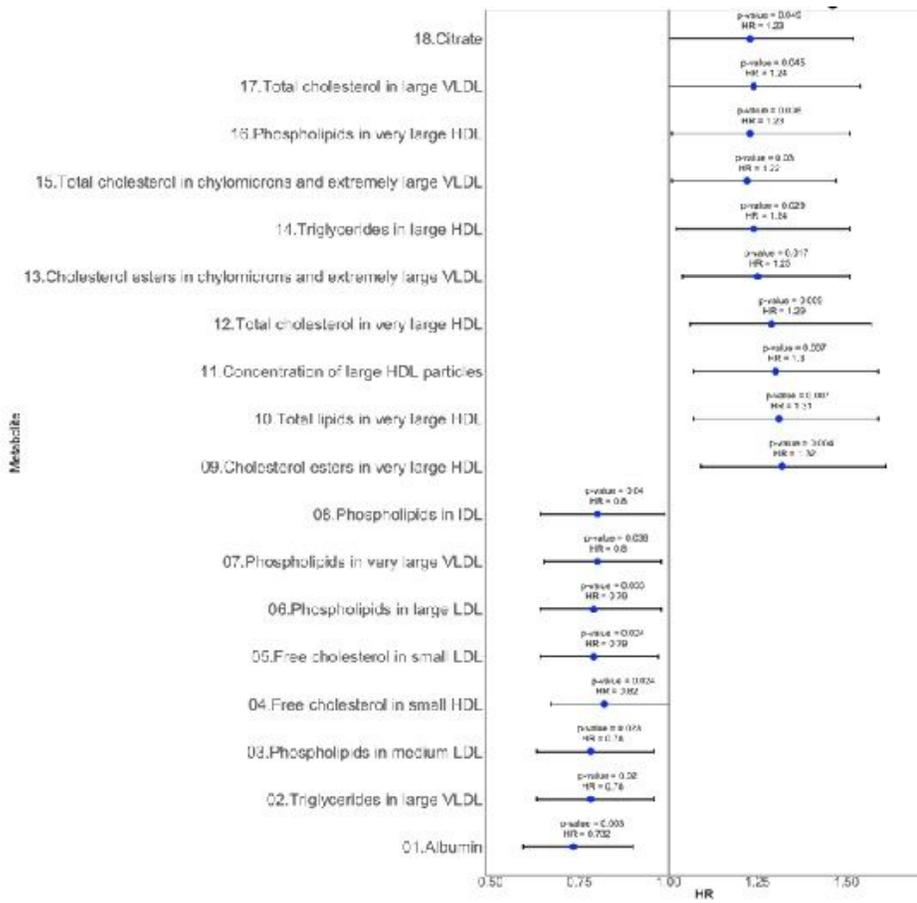


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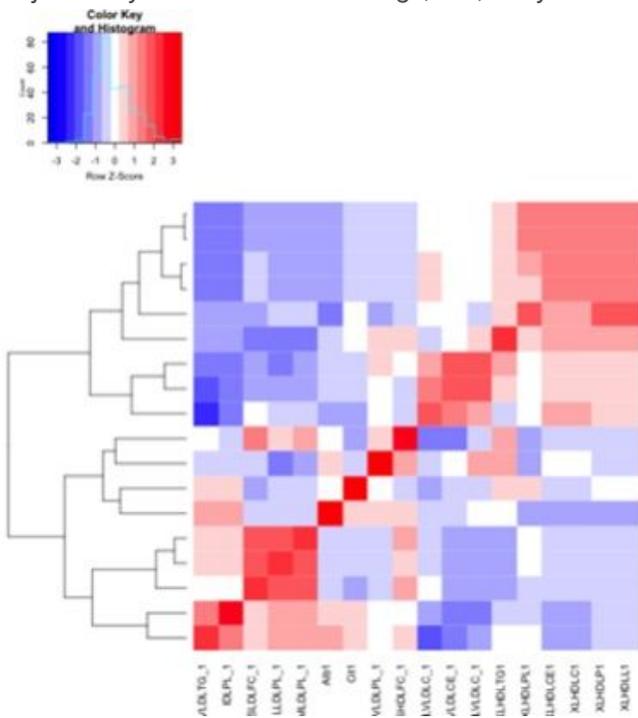


Figure 2

Correlation matrix with eighteen metabolites associated with normal glucose tolerance regression

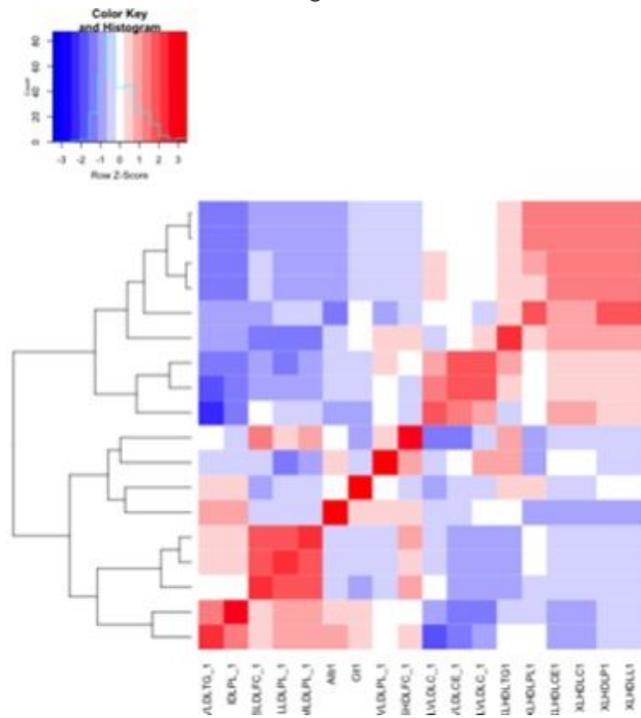


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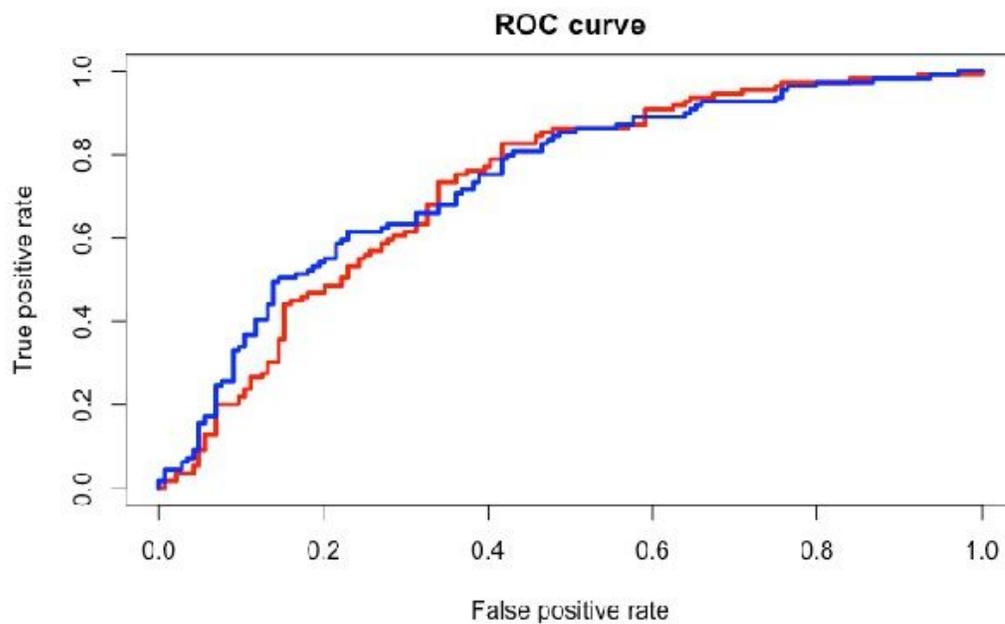


Figure 3

Area Under the ROC curve predicting the regression to normoglycemia. Red line represents the predictive capability of clinical variables (age, body mass index and fasting glucose) for which the AUC was 0.73 (95% CI, 0.66 - 0.78). Blue line represents the model with clinical and metabolomic variables: albumin, citrate, and triglycerides in large HDL 0.74 (95% CI, 0.68 - 0.80, $p=0.485$).

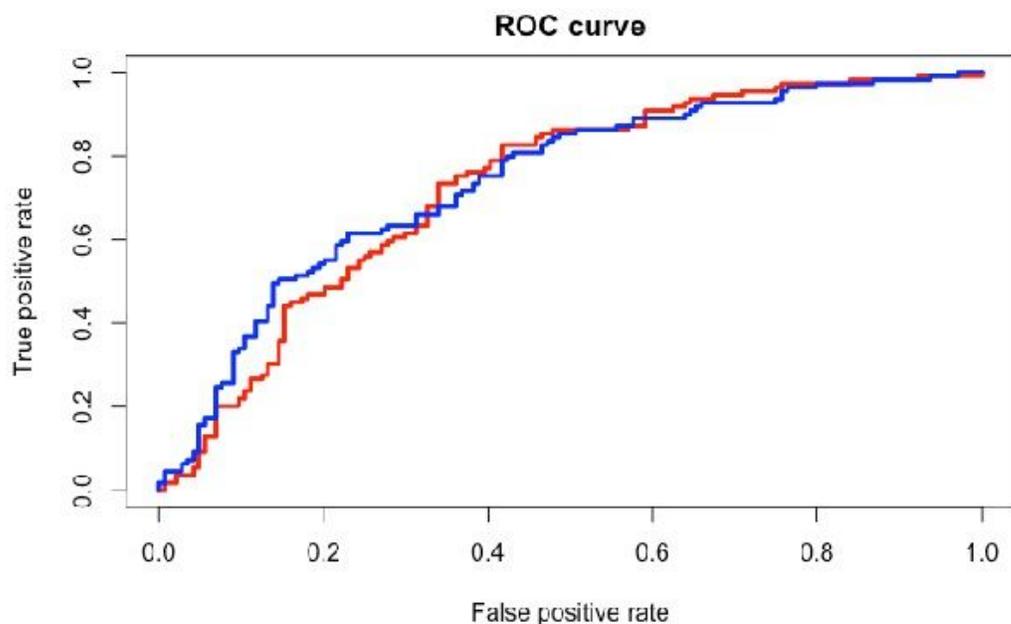


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